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RADIATION EFFECTS IN MAN: MANIFESTATIONS AND THERAPEUTIC EFFORTS

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13. ABSTRACT

The goal of our program has been to obtain new information regarding the pathophysiologic, psychologic, immunologic, hematologic, and biochemical effects of total- and partial-body irradiation in human beings. The patients are irradiated, all of whom have inoperable, metastatic carcinoma but are in relatively good health, provide us with the opportunity to study multiple facets of the effects of radiation in man rather than in experimental animal. As we and many other laboratories have discovered, extrapolation of results from laboratory animals to man to be fraught with error. We have continued our search for a suitable biological dosimeter in human beings. The data contained in this report will suggest several potential biological dosimeters previously considered to be of some value have not fulfilled this expectation.

Biochemical and psychological studies have extended the findings of our previous report in depth and scope. Several new biological dosimeters are under evaluation.

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FOREWORD

This report was prepared by the following members of the University of Cincinnati College of Medicine:

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These studies were performed in conformation with the "recommendations guiding doctors in clinical research" as stated in the Declaration of Helsinki of the World Medical Association (1964).

Research was conducted according to the principles enunciated in the "Guide For Laboratory Animal Facilities and Care, " prepared by the National Academy of Sciences, National Research Council.

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INTRODUCTION

The current report summarizes our work from 1 May 1969 through 30 April 1970 and details certain specific fields of investigation in the human being. Most of these data and a survey of our earlier work were presented by Dr. Edward B. Silberstein in an invited paper at the IAEA-WHO Conference in Paris on 24 June 1970.

Damage to biological systems due to ionizing radiation is the result of deposition of energy within the tissue of the animal irradiated. Since the victims of the explosion of a nuclear weapon may receive injury from blast and burn, as well as from radiation, and all three modalities involve the transfer of energy to tissue, the importance of finding a radiation-specific dosimeter cannot be overestimated. However, one might expect a priori that biochemical changes would be relatively nonspecific.

Our laboratory has looked at a wide variety of pathophysiologic changes induced by irradiating human beings with whole- or partial-body radiation. These studies were all performed on ambulatory human subjects in whom a control period preceded the irradiation. Most of the patients had inoperable metastatic carcinoma which was not amenable to conventional chemotherapy. Nevertheless, these patients were all clinically stable, many of them working daily. Several of the subjects, apparently tumor-free and clinically normal after regression of regionally irradiated tumors (Ewing's tumor), received prophylactic whole-body radiation.

The radiation technique employed in these patients as well as our chromosome culture method are found in appendixes A and B.

Once again our attention has turned to the evaluation of chromosome aberrations. When the many human studies are evaluated, there is a suggestion that variations in dose-response data may be a function of dose rate, an aspect of human radiobiology which requires more attention than it has received to date. The applicability of the method of chromosome culture is evaluated in regard to

its use as a dosimeter, and certain problems requiring investigation are delineated.

Etiocholanolone continues to be of interest in determining the response of the granulocytes and may well be useful clinically in warning of impending leukopenia.

It has been disappointing to find that the excretion of deoxycytidine in the urine of man is not nearly so useful a biological indicator as it was in the rat. Deoxycytidine deaminase is present in human plasma but not in the rat. Also, high urinary values of deoxycytidine are found occasionally in unirradiated malignancies, in burns, and to some degree in orientals. A number of substances involved in the metabolism of nucleic acids have been studied in this laboratory; e. g., beta-aminoiso-butyric acid (BAIBA) and taurine, without finding an exclusive association between radiation and increased breakdown of these metabolites Because the nucleus seems so vulnerable to radiation, some new approaches to this problem are being formulated.

Elevations of urinary and serum amylase seem to be related to irradiation of the parotid and possibly not of the pancreas. The presence and type of dose-response relationship and the specificity of this reaction will require further study. If this relationship continues to be observed and if other enzymatic changes in other organs can be identified, it is conceivable that "enzymatic biopsy" may yield information on the distribution and doses received under circumstances of nonuniform exposure.

The continuing investigation of cognitive-intellectual functioning and emotional reactions presents data on a larger group of patients than have been studied within this year. Of considerable interest is evidence of a rise in cognitive malfunctioning immediately after radiation, disappearing after day 3. The more intelligent individuals show less dysfunction than do those with basic intellectual defects.

Since these studies emphasize the uniqueness of the human being in the further understanding of radiation effects both in regard to diagnosis and therapy, it will be of continuing value to enlarge on studies of this kind.

CLINICAL STUDIES

Chromosome Aberrations

The use of chromosome aberrations as a biological radiation dosimeter began with the classical experiments of Saks (1, 2, 3) and of Lea and Catcheside (4) on the quantitative relation between the change in yield of radiation-induced chromosome aberrations and increasing dose. Although these studies were performed 30 years ago, this use of chromosome aberrations remains a highly controversial area. There are today cytogeneticists who believe that the kinetics of dose-response studied in these early experiments are inapplicable to man, because the earlier work involved plant nuclei having large chromosomes and low chromosome numbers (5), while man has 46 chromosomes (6) of small individual volume.

To justify the use of any dosimeter, one must be able to reproduce the calibration curve between the dose of radiation and the response of the test system. Furthermore, one must be able to employ the dosimeter to ascertain to what extent the test system has been exposed to radiation; that is, one would like to know whether the biological system to be examined has received an homogeneous dose of radiation distributed uniformly or an inhomogeneous dose interacting with all or part of that system. Continuing disagreement about the calibration of human lymphocyte response to radiation and the problem of distinguishing whole- from partial-body radiation with this system do not permit utilization of radiation-induced chromosome aberration dose-response curves in a rigorous fashion to date. However, there have been several instances where chromosome analysis has been useful in proving that high doses indicated by radiation badges were in fact not received by the individuals wearing them (7, 8). Furthermore, chromosome aberrations caused by radiation in man are not affected by ambient temperature and pressure as are physical dosimeters (for which corrections can usually be made).

Study of radiation effects on mammalian cells is complicated by the fact that radiation sensitivity of cells varies with the stage of their cell cycle. Repair time of chromosome breaks has been found to be 90 minutes in the G_1 (postmitotic

presynthetic phase) and S (DNA synthesis) phase but 60 minutes in late S and G_2 (postsynthetic premitotic phase) (9). Furthermore, there is interspecies variation in radiation-induced chromosome aberration curves (10), with the extrapolation from animals to man being somewhat hazardous. This variation is probably related to differences in chromosome number and volume between species examined. One would like to use primates in this research, but ideally one must find an animal that has the same chromosome number and configuration as man in order to be confident of the extrapolation.

Human lymphocytes can be stimulated to divide in vitro (11) where the mitosis can be arrested with colchicine and then analyzed under the microscope. Furthermore, 99.9 percent of human lymphocytes are in the G_1 growth phase (12), and this is a period of uniform radiation sensitivity (13). Thus, numerous investigators have employed this system to obtain dose-response curves (5, 14-24). These curves were usually derived from in vitro studies. The relationship of in vivo to in vitro experiments will be discussed below.

But which "response" should be studied? As noted above, radiation causes chromosome breakage in nucleoprotein or polynucleotide chains (25) which may or may not be followed by recombination between broken ends (1-3). An alternative mechanism has been proposed by Revell, the so-called "exchange-first" hypothesis (26). The aberrations produced (if broken ends do not rejoin perfectly) are of two types, chromatid and chromosome aberrations. Increments in the latter, which occur when chromosomes are in the G_1 pre-DNA synthesis phase, are the types observed in the lymphocyte system with which we are concerned. Breakage and recombination occurring in G_1 will be duplicated during the S-phase so that both chromatids of a chromosome will show the abnormalities when viewed in metaphase. Therefore, abnormalities in just one of a pair of chromatids are unrelated to radiation in the system. Figures 1 and 2 indicate the common chromosome aberrations. Chromosomes with more than two centromeres have been observed. The dicentric and ring forms are far easier to score than the more subtle translocation and inversion types where slight changes in centromere position may be the only hint of preceding breakage. Furthermore, in one study the sum of all aberrations apart from dicentrics made up 60 to 70 percent of the

CHROMOSOME-TYPE ABERRATIONS

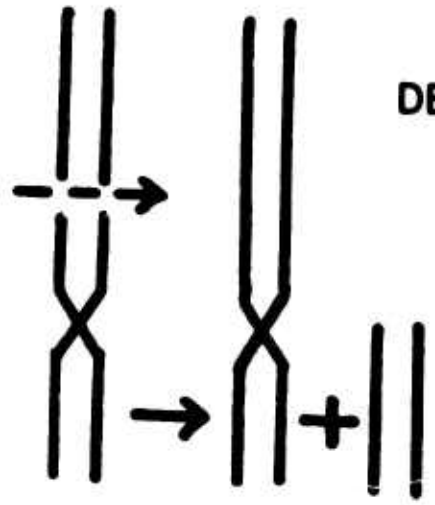


Figure 1.

CHROMOSOME-TYPE ABERRATIONS

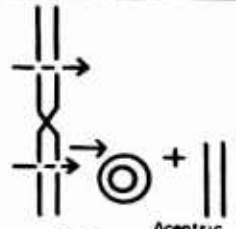
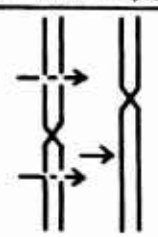
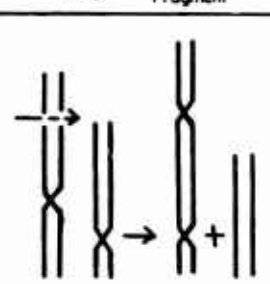
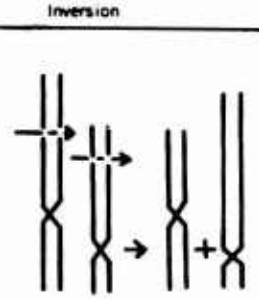
	ASYMMETRIC ABERRATIONS (leaves acentric fragments)	SYMMETRIC ABERRATIONS (more subtle morphologic change)
INTRA-CHANGE	 Ring; Acentric Fragment	 Inversion
INTER-CHANGE	 Dicentric; Acentric Fragment	 Translocation

Figure 2.

dicentric yield (27). With each dicentric, one should also identify an acentric fragment which would be lost after one division. Its presence is evidence that one is indeed observing the first post-phytohemagglutinin-induced mitosis. Thus, one may use far less experienced laboratory personnel for the chromosome analysis and it can be performed far more rapidly than a search for symmetric aberrations would allow. Since virtually all of the lymphocytes containing the chromosome aberration are not dividing, it may be expected that even the unstable dicentric and ring aberrations persist for a considerable period if the cells containing them are not activated by an endogenous mitogen (28), and if they are long-lived lymphocytes as opposed to the lymphocyte population with a brief lifespan (29, 30).

For the purpose of dosimetry, however, lymphocyte cultures should be made as soon as possible. There does not appear to be a difference in aberration yield over 24 hours postirradiation (5, 7, 31). After 48 to 72 hours, the lymphocyte count in an irradiated human has usually fallen so low that finding enough mitoses to count (50 to 200) is more difficult. However, Bender has stated that "aberration levels measured in peripheral leukocytes remained relatively constant for the first 3 or 4 weeks after radiation" (22). The kinetics of this biological dosimeter bear careful consideration because of the current controversies surrounding the dose-response relationship. The rings and dicentrics we measure are each formed from two separate breaks in one or two chromosomes respectively (Figure 2). These aberrations, when induced by sparsely ionizing X-rays or gamma rays, should therefore usually require two separate photons to interact with the environment of the chromosome, and thus the aberration frequency should increase with the square of the radiation dose; whereas aberrations requiring but a single interaction should increase in linear relationship to the radiation dose. Only an occasional, well-placed, single photon should lead to two separate chromosome breaks. Radiation containing particles with high linear energy transfer (L.E.T.), such as neutrons, produce a much larger volume of ionization per particle; and therefore, for high L.E.T. radiation dicentrics and rings, increase as a linear function of dose (32). In other words, the neutron and other particles with high L.E.T. generally produce more than one

chromosome break per neutron. However, for sparsely ionizing radiation, one might anticipate the yield of rings and dicentrics to be represented by the quadratic equation $Y = c + aD + bD^n$ where Y is the yield of dicentrics and rings after 48 hours of culture, c is the spontaneous frequency for rings and dicentrics (approximately one in 5,000 normal cells), a is the coefficient of aberration for a single photon inducing rings and dicentrics, b is the coefficient for two hit exchanges, D is the dose of radiation in rads, and n is equal to approximately 2 (33). Or, if one believes that two separate ionizing events are always necessary for the production of dicentrics and rings, and since these abnormalities are essentially absent in a "normal" population, one may try to fit the observed data to $Y = bD^n$, assuming n will be close to 2. Tables I and II summarize available data for cells analyzed after 44 to 52 hours of culture time for rings plus dicentrics or dicentrics alone (since the ratio of dicentrics to rings is usually about 5 to 1). Studies performed on cells cultured for longer periods of time (for example, reference 14) are excluded despite their historic and scientific significance. (See paragraph 2 below.)

The discrepancies in these results are striking. How can they be explained? We may offer several reasons for the variations in data.

1. There remains uncertainty whether the chromosome response to sparsely-ionizing radiation (X-ray and gamma ray) follows linear, quadratic, or power-law (dose-squared) kinetics, so that there cannot yet be agreement on a calibration curve after 8 years of experimentation. The data may be fitted by several experimental models.

2. Technical differences do not appear to be at the heart of the matter if lymphocytes are cultured for no more than 52 hours before fixation, at a time when they are in the first mitotic division (13). Waiting longer will lead to errors in counting by loss of some dicentric and ring chromosomes during second mitotic division and the formation of "artifactual" dicentrics from chromatid anomalies which self-replicate prior to the second mitotic division. Mitotic delay, which theoretically could decrease the number of dicentrics observed at 50 rads, does not seem

TABLE I

COEFFICIENTS FOR THE EQUATION

$Y = c + aD + bD^n$

FOR RINGS AND DICENTRICS
(Quadratic Formula)

a (rad^{-1}) x 10^{-3}	b (rad^{-2}) x 10^{-6}	n	Radiation Rate (rads per min)	Type of Radiation	Ref.
3.42 ± 0.17	3.51 ± .68	2 (assumed)	17.5 - 230.5	250 kVp X-rays	5
2.50 ± 0.74	1.35 ± 2.24	2 (assumed)	98 - 200	250 kVp X-rays	17
1.78 ± 0.20	2.30 ± 0.53	2 (assumed)	19 - 292	1.2 mev gamma rays (^{60}Co) in vitro	17
0.52 ± 0.13	1.72 ± 0.27	2 (assumed)	0.04 - 0.55	1.2 mev gamma rays (^{60}Co) in vitro	17

TABLE II

COEFFICIENTS FOR THE EQUATION

$Y = bD^n$

FOR DICENTRICS AND RINGS

b (rad^{-2}) x 10^{-6}	n	Radiation Rate (rads per min)	Type of Radiation	Ref.
1350 ± 280	1.17 ± 0.04	17.5 - 230.5	200 kVp X-rays in vitro	5
0.992 - 1.686	1.97	67	250 kVp X-rays partial-body radiation in vivo	7
12.74 ± 0.15	2.15 ± 0.07	50 R* per min.	250 kVp X-rays in vitro	19
5.7 ± 0.5	2 (assumed)	100 - 200	1.9 Mev. X-rays in vitro	24
---***	0.92 ± 0.4	1	2 Mev. X-rays whole-body radiation	7
30	1.82	100	250 kVp X-rays in vitro	34**
10	1.87	100 - 200	1.9 Mev. X-rays in vitro	24 as fitted by 34
1200	1.17	17.5 - 230.5	250 kVp rays in vitro	5 as fitted by 34
520	1.13 ± 0.61	1	2 Mev. X-rays whole-body radiation	35
42.2	1.88 ± 0.54	1	2 Mev. X-rays whole-body radiation (same patients as above, cells taken 24 hrs. after irradiation)	35
57 ± 36.4	1.52 ± 0.10	0.04 - 0.55	1.2 Mev. gamma rays (^{60}Co) in vitro	17
665 ± 240	1.24 ± 0.06	19 - 292	1.2 Mev. gamma rays (^{60}Co)	17
1170 ± 1540	1.16 ± 0.23	98 - 200	250 kVp rays in vitro	17
8.50	1.94	----***	1.5 - 1.9 Mev. X-rays, in vitro	38
25.5	1.78	----***	1.2 Mev. gamma rays (^{60}Co) in vitro	38
81.14	1.66	----***	200 kVp X-rays in vitro	38
1039	1.24	----***	14 Mev. neutrons in vitro	38

*Roentgens air dose
**Dicentrics only
***Information not given

to be a problem in vitro at doses up to 500 rad (13, 36). Temperature variations of as little as 1^{o} C. may have marked effects on influencing the rate of cell response to phytohemagglutinin (37). Two laboratories whose most recent results diverge widely used identical techniques, however (17, 19). One must obviously be careful of observer bias in analyzing slides, and no one should count only dicentrics in cells that also contain an acentric fragment as noted above, indicating that one is indeed observing the first postradiation mitosis. If one counts more subtle aberrations, such as breaks, translocations, and inversions, there is much greater danger of erroneous subjective interpretation. Data on gamma or X-irradiated cultures (5, 17, 34) give lower power functions and higher coefficients for rings and dicentrics than data on irradiated whole blood (24).

3. Lymphocytes are inhomogeneous with respect to function and lifespan, only about 20 percent of them having a lifespan of 72 to 96 hours, many living much longer (30, 39, 40). Thus, one might hypothesize this as a cause of significant variation between donor lymphocyte aberrations in response to radiation injury and to stimulation by phytohemagglutinin. However, the variation in response between individual blood donors does seem quite small in vitro (14, 27) and in vivo (31) when cultures are begun within 24 hours of irradiation. Thus, although there may be significant differences in varieties of lymphocyte populations between individuals, these populations all seem to respond similarly to radiation injury.

4. Dose rates vary widely in the experiments noted in table II. Our own dose rate is rather low, 3.5 to 6 rads per minute. The aberration yield was clearly lower with dose rates of 0.04 to 0.55 rads per minute than with rates of 17.5 to 230.5 rads per minute in a recent series of experiments (5, 27) employing the same techniques in all cultures. The yield in the range from 17.5 to 230.5 rads per minute was essentially identical (5).

5. The relative biological effect (RBE) varies because different modalities of radiation transfer different amounts of energy to the cells irradiated. Therefore, different calibration curves would seem necessary for high- and low-energy gamma or X-rays and for neutrons. It is generally agreed that neutrons give a linear dose response because of their high linear energy transfer. The RBE of 14.1 million electron volt (Mev.) neutrons compared to 250 kVp X-rays has been set at 1.9 (41); whereas for 0.7 Mev. neutrons, an average value of 3 to 3.5 was found by a different laboratory (23, 32). RBE of Cobalt-60 gamma rays was found to be 0.8 (17) when compared to 250 kVp X-rays. The problem of chromosome biologic dosimetry with mixed radiation from reactors or nuclear weaponry thus becomes increasingly complex.

6. Because fewer chromosome aberrations after irradiation are found in an hypoxic environment (42), people with relatively low arterial oxygen saturation might have more radio-resistant chromosomes than those with normal arterial oxygen tension.

7. Another problem with the chromosome system is that of saturation of available sites where breaks can occur at higher radiation doses (24, 43, 44). Thus, at doses over 500 rads in vitro, the dose-response kinetics have indicated saturation in dicentric and centric ring yields (24).

8. With few exceptions, the calibration curves published to date have been from in vitro studies and the in vivo radiation has been with doses of 50 rads or under (7, 35). Many use a culture time of 72 to 90 hours, which we know is too long (45, 46). Our preliminary data from one patient given whole-body irradiation of 100 rads and three at 200 rads are shown in figures 3 and 4 (Silberstein). In vivo we find a much lower aberration response than has been seen in vitro. (Our patients all had inoperable metastatic carcinoma and were clinically stable; they were hematologically normal except for frequent mild anemia. The radiation technique and chromosome culture technique appear in appendixes A and B. The patients were ambulatory and some were disease free,

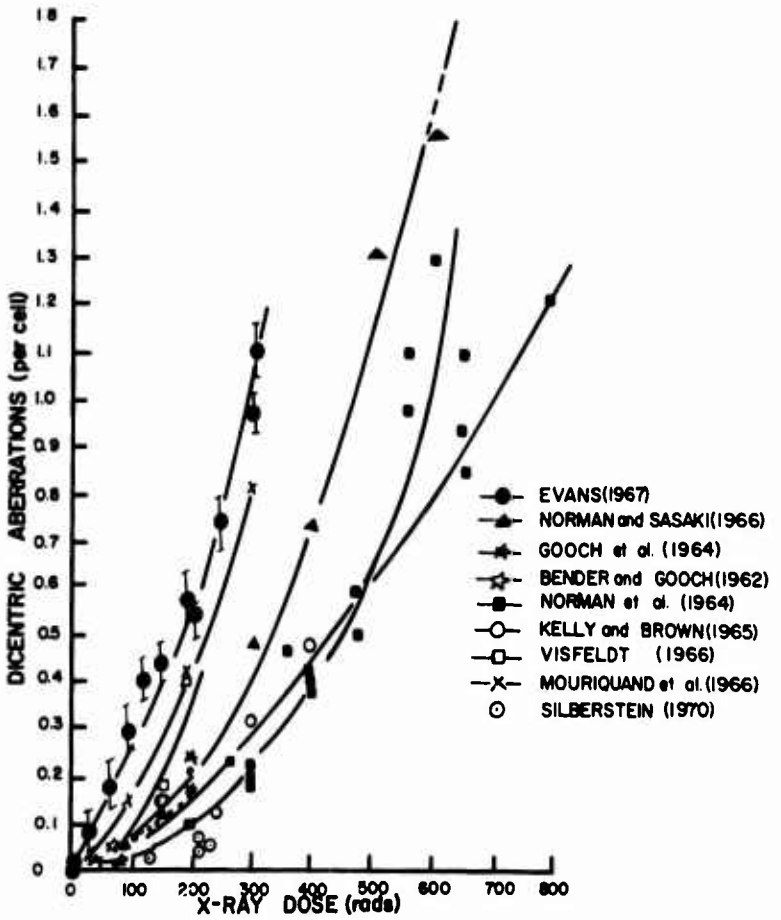


Figure 3. --The Effects of Increasing X-Ray Doses on the Number of Dicentric Chromosome Aberrations in Human Peripheral Blood Leukocytes (Courtesy Peter C. Nowell (37)). Modified by additional data of E. B. Silberstein obtained in this study.

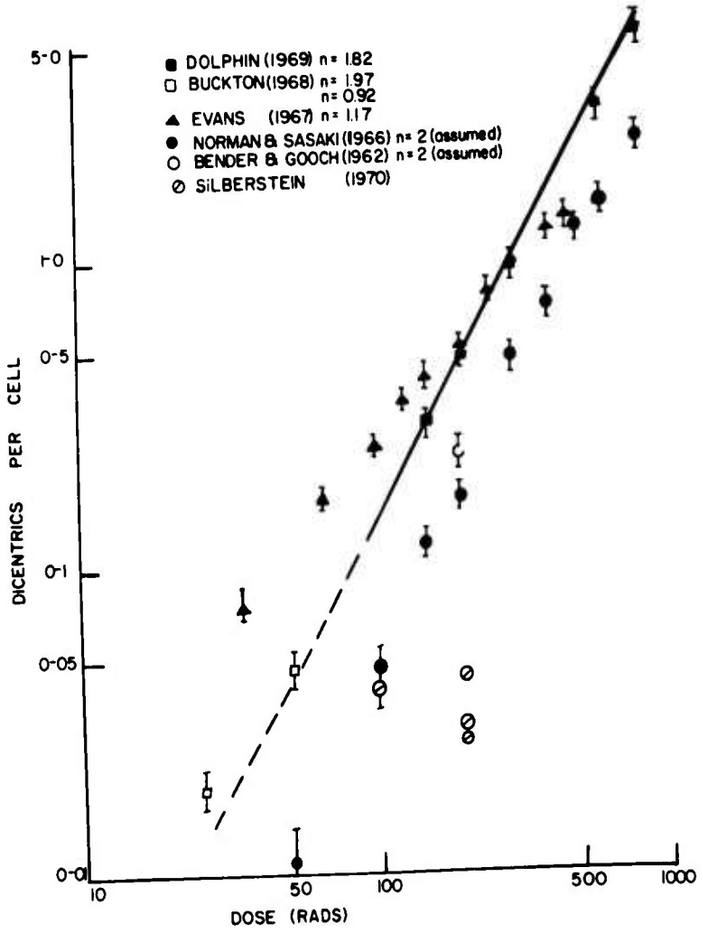


Figure 4. --The Effects of Increasing X-Ray Doses on the Number of Dicentric Chromosome Aberrations in Human Peripheral Blood Leukocytes.

receiving prophylactic irradiation.) In vivo damaged lymphocytes may be rapidly removed from the circulation, and since our radiation time may extend over an hour, we might miss seeing many cells containing chromosome aberrations. However, our blood samples are obtained from the patient just before and immediately after irradiation. Our dose rate, 3 to 6 rads per minute of Cobalt-60 gamma irradiation, is lower than that employed in the other in vivo data (7, 35). Perhaps there may be greater resistance to radiation-induced chromosome breakage in vivo than in in vitro or more rapid repair of chromosome breaks in vivo. In vivo-in vitro comparisons have been made largely from partial-body or inhomogeneous irradiation which has been extrapolated to whole-body equivalents (22, 40, 47) with moderately good agreement.

9. Even if all the difficulties in calibration listed above can be overcome, we are still left with the problem of inhomogeneous exposure which is always difficult to quantitate exactly. A heterogeneous dose of radiation will obviously yield fewer aberrations than the same dose given over the whole body. The numbers of rings and dicentrics found will be related both to the volume of tissue irradiated and to the number of lymphocytes contained within that tissue. For example, there are far more lymphocytes in a 125-gram spleen than in a 1, 400-gram human brain. The mean residence time of the human lymphocyte in the blood has been calculated at 4.7 to 7.5 minutes by one estimate (45). If lymphocytes all circulate very rapidly back into the intravascular compartment, then blood from a person with partial-body radiation delivered over some significant period of time might show the same incidence of chromosome aberrations as if it had been delivered over the whole body. This does not occur when 300 rads is delivered homogeneously over a 2-hour period to the lower half of the body (31).

10. Other agents, such as viruses and drugs, may cause chromosome aberrations. In addition to the nonspecificity of the test system, there is always the possibility that the individual has received prior radiation of

which there is no record. The kinetics of dose-response are quite important in interpreting inhomogeneous exposure. For single-break aberrations, one might theorize that 1, 000 rads distributed over 10 percent of the body might give the same chromosome-aberration response (after time for complete mixing of irradiated and unirradiated cells) as 100 rads to the whole body, assuming of course that the distribution of lymphocytes is uniform throughout the entire body. However, for rings and dicentrics this logic does not hold if one assumes dose-squared kinetics. For, if one examines the effect of 1, 000 rads over 10 percent of the body in terms of the dicentric and ring yield, one should find 10 times as many rings and dicentrics as single-break aberrations. This is because the ratio of $(1, 000)^2$ to $(100)^2$ is 100 to 1 so that even after total mixing of radiated with unirradiated cells after an exposure of 1, 000 rads to 10 percent of the body, there is dilution of the ratio of dicentric ring to single-break aberrations from 100 to 1 to 10 to 1. This logic has been employed to confirm inhomogeneous distribution in a radiation accident (22). Dolphin (34) has used the Poisson distribution of dicentrics at a given radiation dose (24) to construct histograms to predict the fraction of the body irradiated, although our preliminary data with excellent dosimetry for partial-body radiation do not confirm his theoretical discussion (31), as the aberration frequency appears to be much lower.

Clearly much more in vivo data with good dosimetry are required. We are pursuing this goal at whole-body radiation doses up to 250 rads with even higher doses planned with the support of marrow autotransfusion and laminar-flow "sterile" rooms. Large-volume partial-body irradiation is also being performed to learn more about the efficacy of chromosome aberrations as a radiation dosimeter in the more frequent situation of inhomogeneous exposure. With a linear accelerator, we hope to study the effects of various dose rates in vivo as well.

Etiocholanolone Studies of Granulocyte Reserves in Irradiated Patients

The absolute lymphocyte count of the peripheral blood drops much more rapidly than do the counts of the cells produced in the erythroid, myeloid, and megakaryocytic series. Similarly, as noted above, lymphocyte chromosomes may be analyzed immediately after radiation for radiation-induced aberrations. Chromosomes of the myeloid and erythroid series may be analyzed also. Here, however, the situation is even more complex than with the lymphocyte series because bone-marrow cells are in all stages of the cell cycle (G_1, S, G_2, M) while 99.9 percent of the lymphocyte are in G_1 (12). Since radiation sensitivity varies during the cell cycle, interpretation of observed aberrations is even more fraught with error than in the lymphocyte system. How then can we evaluate failure of the myeloid series soon after irradiation? Our laboratory has chosen to examine bone-marrow granulocyte reserves for this purpose.

Etiocholanolane, a naturally occurring steroid metabolite of adrenal and gonadal origin, is a potent stimulus to leukocytosis in man (49, 50). The increment is solely in cells of the granulocytic series, largely neutrophilic-polymorphonuclear granulocytes (51). At a dose of 0.10 milligrams per kilogram of body weight given intramuscularly, the normal average maximum granulocyte increase within 24 hours is 5,850 $\pm$ 770 per cubic millimeter in men and 6,700 $\pm$ 1,400 per cubic millimeter in women. The lower limit of the normal granulocyte increment is 2,600 per cubic millimeter. In a series of 151 injections of etiocholanolone we recently analyzed, the maximum increment occurred at 16 hours in 46 percent, at 20 hours in 32 percent, and at 24 hours in 22 percent of the injections. We gave the etiocholanolone at 1600 hours and obtained blood counts at 0800, 1200, and 1600 hours the following day.

The increment in the peripheral blood count after etiocholanolone is the result of mobilization of granulocytes from the bone-marrow reserves (53) and is not merely the result of redistribution of extramedullary cells from marginal pools to the circulating granulocyte pool. Endotoxin has also been used to evaluate bone-marrow reserves (53, 54, 55). Pyrexal, an endotoxin of Salmonella abortus, has been withdrawn from the American market, but a Pseudomonas

product, Piromen, is available for this purpose (54). However, this material must be injected intravenously; endotoxemia may trigger intravascular coagulation, although this side effect has not yet been reported with Piromen. We also prefer etiocholanolone because its only side effects are local inflammation at the injection site and occasional fever never exceeding 2° C. Also, intramuscular rather than intravenous injection allows a technician to administer this steroid without resorting to venepuncture. As opposed to endotoxin, repeated doses of etiocholanolone can be given without causing reticuloendothelial blockage; it is also nonantigenic (49).

Our patient population has been previously described. When one is dealing with patients who are not entirely "normal," the question arises as to whether this patient population can be compared to normal controls studied by others. However, the fact that the average maximum granulocyte increment prior to radiation in our patients was 6, 200 cubic millimeters (normal average maximum increment 5, 850 to 6, 700) indicates that the two groups are indeed comparable. The maximum increment does not diminish with age. These patients received 100 to 300 rads whole- or partial-body radiation doses (see appendix B for technique).

Fifteen patients have been studied (Table III). In only one did the maximum granulocyte increment become subnormal after the white blood-cell count had fallen below 5, 000 (by 2 days). In 10 of the 15, the fall in maximum granulocyte increment to subnormal levels preceded any white blood-cell count drop.

In six of these 10 whose white counts eventually did go under 5, 000 per cu. mm., the abnormality in etiocholanolone response preceded the leukopenia by an average of 12 days, suggesting that this biological dosimeter may be of significant assistance in giving warning of an impending leukopenia. In four of the 15, maximum granulocyte increment dropped under 2, 500 per cu. mm. on the same day that the white count fell under 5, 000. The subnormal etiocholanolone response generally occurred on days 6 to 9 after radiation. One hundred rads of whole-body radiation were sufficient to cause the test to become abnormal as were 150 rads to approximately 40 percent of the marrow volume.

TABLE III

ETIOCHOLANOLONE AS A PREDICTOR OF LEUKOPENIA

Patient	Dose (rads)	Day of first etiocholanolone response under 2600 per cu. mm. (white blood count per cu. mm. on that day in parenthesis)	Day of white blood count falling under 5000 (or by at least 1000 if control count is below 5000) (white blood count per cu. mm. in parenthesis)
099	250 WBR*	6 (3700)	6 (3700)
095	200 WBR	6 (4300)	6 (4300)
087	200 WBR	7 (5900)	9 (3400)
091	200 WBR	9 (9000)	24 (4900)
098	200 WBR	6 (4900)	6 (4900)
093	150 WBR	8 (4300)	6 (3500)
088	150 WBR	2 (9400)	7 (3300)
096	100 WBR	6 (6400)	34 (4900)
097	100 WBR	6 (4100)	6 (4100)
086	100 WBR	8 (10, 200)	*****
102	200 M-P**	6 (11, 000)	20 (2500)
092	150 M-P	9 (4700)	27 (2300)
089	200 UBR***	1 (9200)	*****
094	150 UBR	8 (7400)	12 (4300)
100	300 LBR****	9 (10, 000)	*****

*WBR = Whole-body radiation
**M-P = Manubrium to pubis
***UBR = Radiation of the half of the body above the xiphoid
****LBR = Radiation of the half of the body below the xiphoid
***** = White count always over 5000 per cu. mm.

The etiocholanolone response was less helpful in predicting recovery, becoming normal before the white count had returned to normal levels in half the patients who had leukopenia. The etiocholanolone response returned to normal in all patients by 9 weeks at the latest (range 6 to 62 days).

The measurement of the maximum granulocyte increment postradiation allows one to predict whether an irradiated individual will experience leukopenia. However, the timing, granulocyte count, or granulocyte increment in the initial drop in the etiocholanolone response did not indicate how severe the eventual leukopenia would be.

The lower limit of the sensitivity of this test of marrow granulocyte reserves has not yet been determined, and this is under study now. It is significantly lower than that in a study employing endotoxin where it was found that at least 40 percent of the marrow must be irradiated to dosage levels over 1,500r before the endotoxin response became abnormal (54).

The timing of recovery of marrow reserves resembles that noted in patients with Hodgkin's disease given extensive fractionated radiotherapy (56).

BIOCHEMICAL STUDIES

Deoxycytidine

After the report of a radiation-induced increase in urinary excretion of deoxycytidine (CdR) in the rat (57), our laboratory examined deoxycytidinuria in man as a biological dosimeter (58, 59, 60, 61). Using a sensitive colorimetric technique (59), we found that the urinary and blood deoxycytidine levels of rats were elevated about 6 hours after X-irradiation, reaching a maximum in blood at 9 hours, urine at 12 hours.

Deoxycytidine excretion in the rat was proportional to the amount of radiation up to 200r. Approximately a sixfold increase from the average preirradiation value of 0.7 mg. per 24-hour urine followed 200r. With tritiated CdR labelled on carbon-5 of cytosine, rats irradiated with 200r excreted 21 percent of the total radioactivity, whereas only 13 percent of radioactivity was excreted by unirradiated rats (61, Figure 5). Since specific radioactivity of CdR isolated from the urine of irradiated rats decreased twofold to sixfold as compared with that of CdR in the urine of unirradiated rats, the free CdR pool size was increased in the irradiated rat (Table 4). This radiation-induced CdR excretion could be suppressed with serotonin and L-cysteine, the respective dose reduction factors being 1.7 and 1.5 for this variable.

Man, however, excretes a much smaller quantity of CdR in his urine than does the rat. An average preirradiation value of 0.007 mg. of CdR per 24-hour urine was found in man (Table V) as compared to 0.7 mg. in the rat. The low CdR excretion in man may be caused by the activity of a CdR deaminase in human plasma (31) and liver (62). However, the range in our cancer patients was 3.9 to 26 micrograms for 24 hours (Table VI). After whole- or partial-body radiation at a dose of 150 rads or above, CdR excretion rose 50 to 350 percent on day 1 postirradiation, returning to normal on day 2 (Table VI). However, this is not a dosimeter specific to radiation injury. A patient with lymphoepithelioma and several burned patients also showed abnormally high urinary CdR excretion in proportion to the severity and extent of the burn (Table VII). Thus,

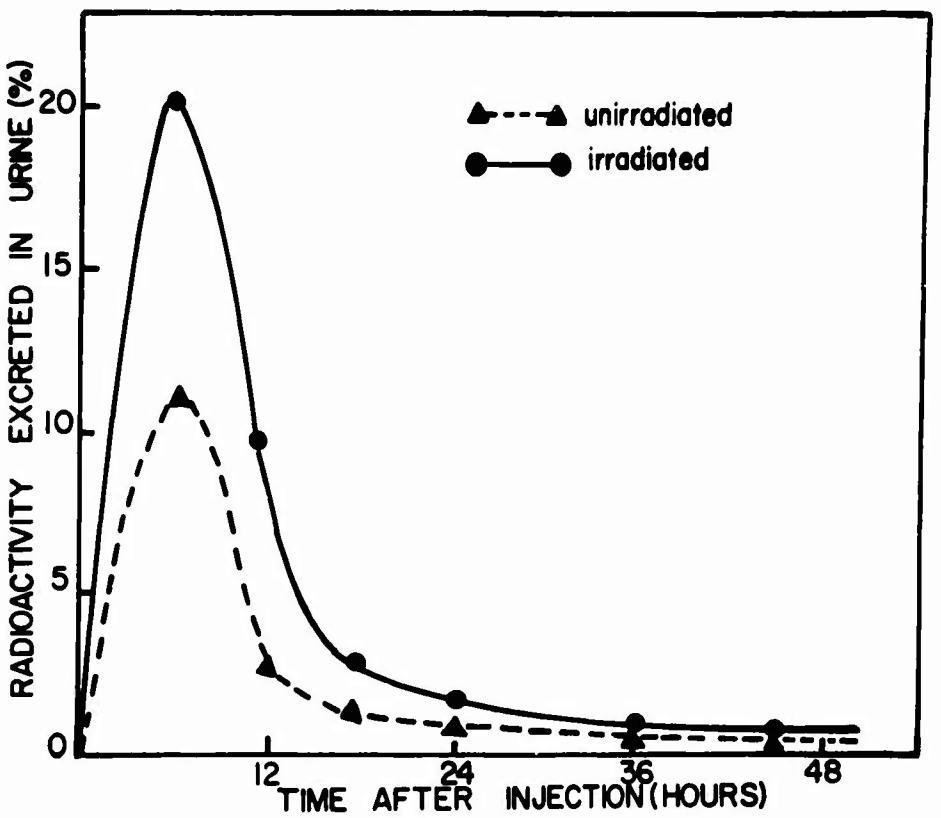


Figure 5. --Effects of Irradiation (200r) on the Excretion of Tritiated CdR in Rats.

TABLE IV

^{3}H-CdR EXCRETED IN 24-HOUR URINE BY RATS

Rat No.	Preirradiation		Postirradiation	
	Specific Radioactivity (CPM/mg.)	Total excreted (mg./day)	Specific Radioactivity (CPM/mg.)	Total excreted (mg./day)
1	192, 000	0.60	61, 000	5.13
2	179, 000	1.04	31, 000	7.16
3	141, 000	1.93	83, 000	6.50

TABLE V

CdR DEAMINASE ACTIVITY IN SERUM AND CdR CONTENT IN URINE FROM SELECTED HUMAN CONTROLS

	Subject		Serum CdR deaminase activity (units/mg. protein)	CdR in 24-hour urine (μg.)
	Age	Sex		
1.	6	M	0.46	5.7
2.	8	M	0.96	12.0
3.	9	M	1.02	13.1
4.	9	M	0.65	4.0
5.	12	F	0.71	2.4
6.	22	F	0.37	5.0
7.	23	M	0.38	8.4
8.	25	M	0.71	4.8
9.	28	F	0.94	4.0
10.	28	M	0.51	2.0
11.	29	M	0.43	6.0
12.	30	M	0.59	12.0
13.	51	M	0.98	7.5
Average			0.67 ± 0.24	6.68 ± 3.67

TABLE VI

CdR IN THE URINE OF IRRADIATED PATIENTS

PATIENTS			DOSE	CdR in 24-hour urine (μg.)			
				Preirradiation	Postirradiation (days)		
Case No.	Sex/race/age	Diagnosis	(rads)	average	1	2	3
--	F/W/48	Ca lung	176 local*	6.6	16.7	--	--
--	F/W/54	Ca breast	200 local**	8.5	16.5	--	--
0.92	F/W/60	Ca breast	150 P. Neck to pubis	5.8 ± 1.3	10.0	8.1	--
0.75	F/W/60	Ca ovaries	200 P. lower	5.4 ± 1.1	6.8	6.1	6.0
0.72	F/W/62	Lymphoma	300 P. lower	8.2	15.2	7.7	--
0.82	M/N/49	Ca colon	300 P. lower	8.1 ± 1.8	16.4	5.0	--
0.79	F/W/50	Ca breast	100 total	26.0 ± 5.2	39.0	25.0	12.3
0.81	F/W/52	Bronchogenic Ca	100 total	4.2 ± 0.2	4.4	3.4	--
0.86	F/W/57	Bronchogenic Ca	100 total	3.9 ± 0.9	4.5	4.0	--
0.83	F/W/78	Ca breast	100 total	5.9	9.3	6.5	
0.88	F/N/54	Ca lung	150 total	8.4	27.8	6.4	--
0.77	F/W/63	Ca pharynx	200 total	6.9 ± 0.4	11.9	12.2	14.3
0.78	M/N/55	Bronchogenic Ca	200 total	20.4 ± 4.3	33.0	31.0	--
0.87	F/W/11	Ewing's tumor	200 total	3.9 ± 1.1	5.8	4.8	--

P. = Partial

*To the anterior and posterior mediastinal ports, including the right hilum and both supraclavicular areas in a "T" portal.

**To the internal mammary chain and supraclavicular and axillary regions.

TABLE VII

CdR DEAMINASE ACTIVITY IN SERUM AND CdR CONTENT IN URINE FROM PATIENTS WITH VARIOUS DISEASES

Patients				Serum CdR deaminase activity (units/mg. protein)	CdR in 24-hour urine (μg.)
	Sex	Age	Diagnosis		
1.	M	14	Lymphoepithelioma	1.20	38.0
2.	M	30	Chondrosarcoma (shoulder)	0.54	14.0
3.	F	76	Carcinoma (bladder)	0.66	20.0
4.	F	62	Carcinoma (breast)	0.64	18.0
5.	M	61	Lymphoma	0.20	18.0
6.	F	42	Bronchopneumonia	0.43	6.1
7.	M	19	Paraplegia	0.76	3.9
8.	M	14	Myasthenia gravis	1.12	11.5
9.	F	47	Rheumatoid arthritis	0.54	10.0
10.	M	28	Diabetes mellitus	0.36	5.9
11.	M	12	Body burns (55%)	0.90	32.6
12.	M	16	Body burns (72%)	1.21	57.3
13.	F	28	Pregnant (3 months)	0.64	5.6
14.	F	17	Pregnant (8 months)	0.72	4.3

deoxycytidinuria appears to be related to general tissue catabolism from several causes, including radiation. Other problems in using urinary CdR include variations in excretion due to race (57) and age (63).

Glycoproteins* Including Transferrin; Serum Iron

Serum glycoprotein levels have been reported to have prognostic significance after radiation injury (64). Using preirradiation levels as controls, the concentration of total protein-bound carbohydrates, particularly transferrin and haptoglobin (65), are found to rise to high levels in mice, rats, and dogs who have died after radiation exposure, although survivors showed little change. However, another investigator reported no significant difference between the mean serum glycoprotein concentration in rats' blood 88 to 90 hours after 600r of X-irradiation and their unirradiated controls (66), but this may well be due to the experimental design employed. The measurement of total iron-binding capacity (transferrin) showed no significant rise after irradiation in our patients (Table VIII). Since all our patients survived their treatment, this is consistent with Evans' prediction that lack of glycoprotein rise correlates with survival.

Radiation-induced damage to the erythroblasts in bone marrow should lead to a rise in serum iron as erythropoiesis decreases. Serum iron levels rose over the first 9 days postirradiation in only 20 percent of our patients studied, and the average change overall was an insignificant drop of 17 micrograms per 100 ml. serum (Table IX). Thus, our material does not confirm some promising animal work (67, 68). The diurnal variation in serum iron and the variation in the levels when the serum is taken at the same time daily (as we did) are significant (69, 70) and diminish the value of the serum iron as a dosimeter. The total iron-binding capacity (transferrin) does not have such diurnal variation, apparently (69).

Amylase

Elevated serum-amylase levels (71) after parotid salivary gland radiation have been noted with doses as low as 100r (tumor dose) (72). The amylase rose

*This work is being carried out jointly with A. Evans and his associates at the Armed Forces Radiobiology Research Institute.

TABLE VIII

CHANGES IN TOTAL IRON-BINDING CAPACITY (TRANSFERRIN) FOLLOWING HUMAN IRRADIATION

Patient	Dose (rads)	Changes in total iron-binding capacity (percent)	Day of maximum change postradiation
099	250 WBR*	+ 6%	0
095	200 WBR	- 8%	1
087	200 WBR	-13%	9
091	200 WBR	-16%	9
098	200 WBR	-23%	0
093	150 WBR	-29%	9
088	150 WBR	+ 1%	3
096	100 WBR	+ 6%	6
102	200 M-P**	+ 4%	4
092	150 M-P	- 8%	2
089	250 UBR***	-12%	9
094	150 UBR	-14%	6
100	300 LBR****	- 7%	13

*WBR = Whole-body radiation
**M-P = Manubrium to pubis
***UBR = Radiation of the half of the body above the xiphoid
****LBR = Radiation of the half of the body below the xiphoid

TABLE IX

CHANGES IN SERUM IRON AFTER HUMAN IRRADIATION

Patient	Dose (rads)	Maximum change from preradiation levels of serum iron within 9 days postradiation (percent)
099	250 WBR*	-31%
095	200 WBR	-59%
087	200 WBR	+78%
091	200 WBR	-33%
098	200 WBR	+152%
093	150 WBR	-60%
088	150 WBR	-18%
096	100 WBR	- 6%
102	200 M-P**	-35%
092	150 M-P	-56%
089	200 UBR***	-58%
094	150 UBR	+ 9%
100	300 LBR****	-75%

*WBR = Whole-body radiation
**M-P = Manubrium to pubis
***UBR = Radiation of the half of the body above the xiphoid
****LBR = Radiation of the half of the body below the xiphoid

to a peak value at 24 to 36 hours after irradiation, then declined to normal over another one or two days. The response appears to be organ specific (31, 71, 72), and hyperamylasemia does not result when the patient receives doses to the pancreas (the usual source of serum amylase) comparable to those causing enzyme release from the salivary glands. The amylase released from the damaged glands is at least grossly related to the absorbed dose of radiation (71, 72).

Our data (Table X, Figures 6, 7) confirm these findings for whole- and partial-body radiation in the human. The graphs show serum and urine levels in patients receiving radiation to the salivary glands. The least striking of the three serum responses is in a patient whose parotid glands were not in the radiation field. Only the patient receiving the highest cumulative radiation dose shows elevated urine levels of the enzyme however, suggesting that this is a less sensitive test than serum amylase. Both urinary and serum responses are prompt however, and both diminish as the cumulative radiation dose destroys glandular function. Table X indicates that the sensitivity of this biochemical dosimeter is at least 100 rads. Radiation below the neck does not increase serum amylase in doses up to 300 rads over the pancreas (not on chart). Our laboratory is currently performing agar gel electrophoresis on the serum of irradiated patients to separate the isoenzymes of amylase.

TABLE X

SERUM AMYLASE LEVELS IN IRRADIATED CANCER PATIENTS

Patients				Amylase (Somogi units/100 ml.)				
Case No.	Sex/Age	Diagnosis	Dose* (rads)	Preirradiation Average	Postirradiation (Hours) 2	20	24	48
87	F/11	Ewing's sarcoma	200	112	160	3,000	2,250	750
98	F/45	Ca colon	200	126 ± 15	139	900	1,200	600
95	F/66	Ca colon	200	150 ± 0	150	225	225	---
90	F/80	Ca bladder	150	112 ± 21	120	---	300	180
88	F/54	Ca lung	150	300	360	360	360	---
86	F/57	Bronchogenic Ca	100	87 ± 11	106	600	600	150
96	M/42	Ca colon	100	160 ± 10	257	560	600	300
97	M/65	Lymphoma	100	168 ± 14	138	---	225	225
92	F/69	Ca breast	150 partial[x]	142 ± 6	178	145	133	178
94	F/69	Ca lung	150 partial[x]	180 ± 0	180	180	180	180

*Unless otherwise indicated, the irradiation was to the entire body.

x Base of neck to pubis.

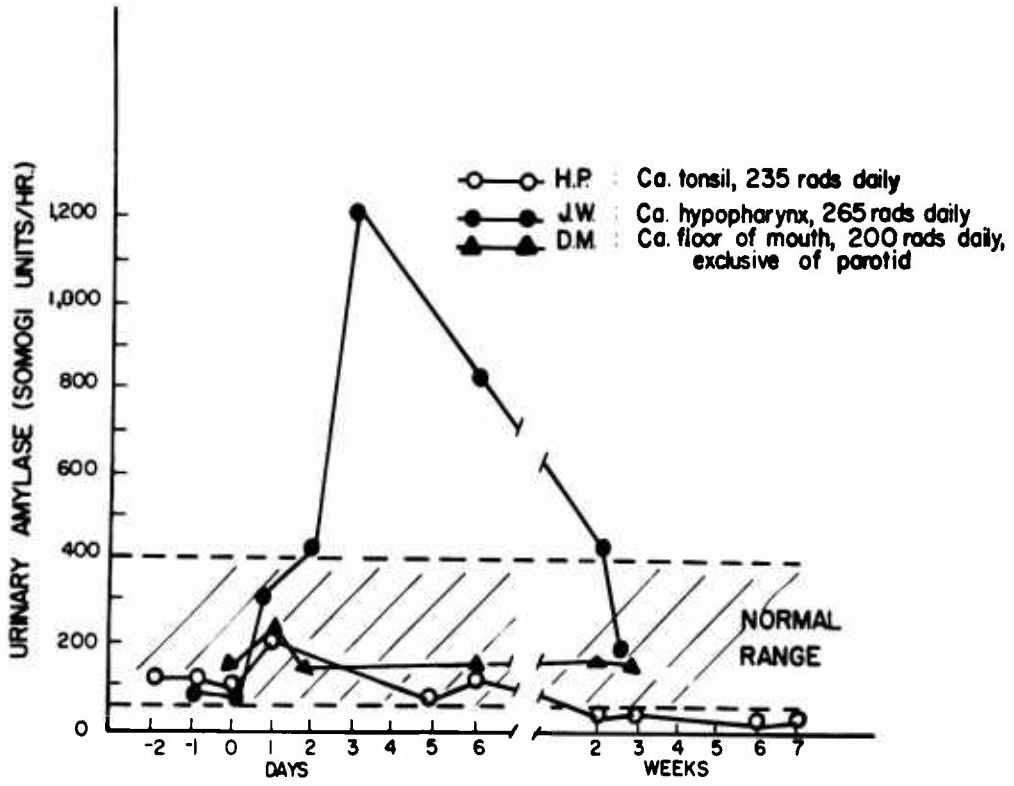


Figure 6. --Urinary Amylase Levels in Patients Receiving Radiation to the Salivary Glands.

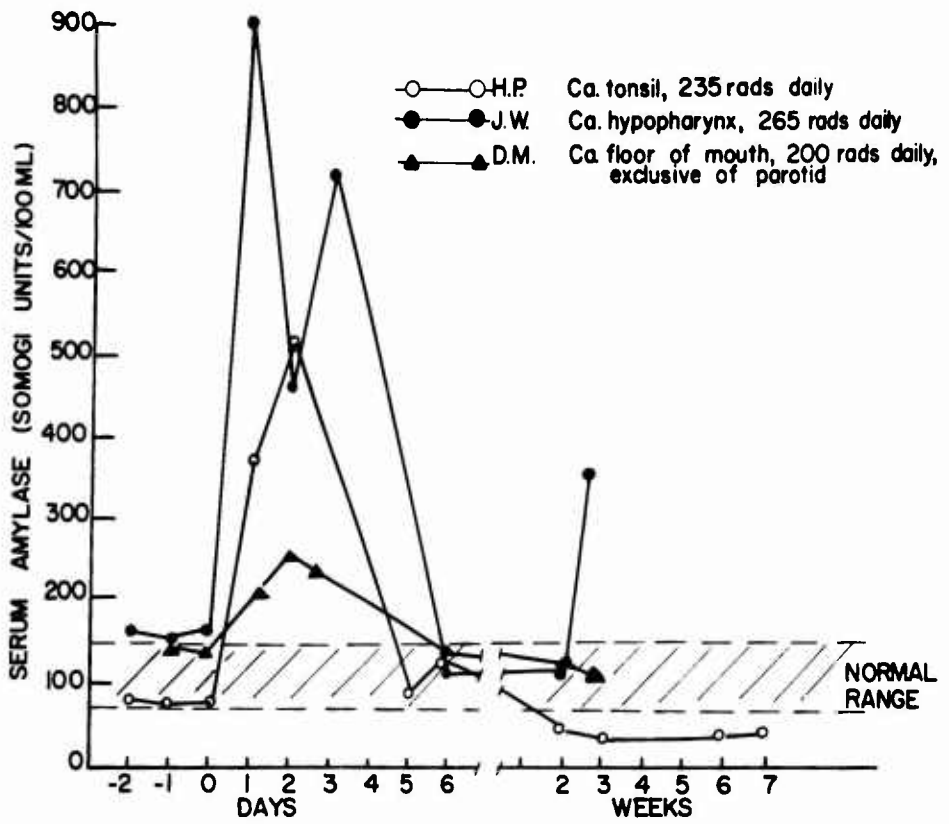


Figure 7. --Serum Amylase Levels in Patients Receiving Radiation to the Salivary Glands.

EFFECTS OF TOTAL- AND PARTIAL-BODY RADIATION ON COGNITIVE-INTELLECTUAL FUNCTIONING AND EMOTIONAL REACTIONS

This report represents a summary of the psychological evaluation of the effects of total- and partial-body radiation on man's cognitive functioning and intellectual reactions. Random sampling error due to the small increments of subjects added to each type of radiation group would result from reporting only for the 11 new patients added since the 1969 report. This summary, therefore, covers the 25 subjects for whom data have been presented in previous years as well as the additional patients, a current total of 36 subjects.

Description data for new patients added in the last year are given in table XI. These new subjects were generally younger, had had more years of schooling, and were somewhat more motivated than patients in previous years of this project. The comparatively better physical condition of these new subjects was attested to by the fact that most were seen for initial and followup interviews either in an office or a home environment rather than in the hospital ward setting which had been the usual testing situation prior to 1969. In addition, only three of our 11 new patients died in less than 100 days following irradiation. This was in sharp contrast to the almost 50 percent low survival rate for earlier years of this study.

A summary of demographic and other pertinent data is given in table XII for the entire group of 36 patients.

The complete methodology followed for the psychological evaluation of all subjects remains as outlined in DASA Report 2168. Data for postradiation days 21 and 35 are being collected but remain too sparse for consistent meaningful appraisal. Where they appear to manifest some stability, they have been included in this year's data presentation.

Personality Characteristics of Subjects in This Study

The Sixteen Personality Factor Test (73) continues to be routinely administered to all subjects during a series of initial interviews prior to sham and actual irradiation. In most respects our group of patients with advanced neoplastic

TABLE XI

BIOGRAPHIC DATA OF 11 RADIATION PATIENTS 1969-1970

Study No.	Sex	Race	Age	Marital[a] Status	Site of Ca.	Type of Rad.[b]	Survival Time[c] (days)	Educ.[d]	IQ[e]
091	F	W	62	W	Colon	T200	52	8	101
092	F	N	69	W	Colon	P150	405 (A)	9	98
094	F	N	67	M	Lung	P150	307 (A)	11	68
095	F	N	58	W	Colon	T200	176 (A)	7	101
096	M	N	43	M	Colon	T100	267 (A)	12	103
097	M	N	67	W	Lung	T100	229	4	89
098	F	N	45	Sep	Colon	T200	119 (A)	8	76
099	M	N	47	Sep	Pancreas	T230	31	10	85
101	M	N	76	W	Colon	P257	124 (A)	8	79
102	M	N	49	M	Lung	P200	22	10	80
103	F	N	45	Sep	Colon	P300	163 (A)	8	76

a - Marital status: W = widowed; M = married; Sep = separated.

b - Type radiation: T = total body; P = neck to pubic area.

c - Survival time: (A) = still alive at time of report.

d - Education: years of elementary and secondary school.

e - IQ was evaluated by means of selected subtests of the Wechsler Adult Intelligence Scale.

TABLE XII

CHARACTERISTICS OF THE SAMPLE

Sex:		
	Males	15
	Females	21
Race:		
	Whites	9
	Negroes	27
Age:		
	$\overline{X}$	60.5
	Range	42 to 84
Marital Status:		
	Married	11
	Widowed	13
	Separated	8
	Divorced	2
	Single	2
Education:		
	$\overline{X}$	6.5 years
	Range	0 to 12+
IQ:		
	$\overline{X}$	84.7
	Range	63 to 116
Type of Radiation:		
	Total-Body Radiation $>$ 150 Rads	N = 11
	Total-Body Radiation $\leq$ 150 Rads	N = 8
	Partial-Body Radiation	N = 17

disease conforms to general adult population norms on this test. However, the differences noted in 1969 which distinguish this patient sample from general adult norms continue to hold true; i.e., these subjects were not only less intelligent than the adult population in general, but they also tended to be significantly more humble, mild, and conforming (Factor E); more taciturn, sober, and prudent (Factor F); more resourceful and self-sufficient (Factor Q_2); and more socially precise and apt to be controlled by their own self-concept (Factor Q_3). In addition, the total group this year was lower than the general population norms on the factor of conservatism (Q_1). It is interesting to note that this group of terminal cancer patients as a whole strongly resembles the personality deviations from normals specified by Cattell, et al. (74), for their sample of depressive patients. Indeed, those of our patients who subsequently will be labeled the short-survival group (i.e., live less than 100 days postirradiation) resemble the pattern for depressives even more than do those defined as the long-survival group. As reported previously, we continue to find that our short-survival group is not different from the published norms on the factor of anxiety and that our long-survival group is indeed somewhat lower on the anxiety factor than the average population.

Depression Rating Scale

In view of the initial resemblance of our group of cancer patients to those with a depressive syndrome, it is not surprising that on the Wechsler Depression Rating Scale (DRS) (75) all patients continue to show at least mild depression throughout the 42 days of the study. The 11 patients added this year all contributed lower average, early depression scores than had been true for the accrued averages of previous years--again a hopeful sign of the increasing better physical and psychological condition of patients currently recruited to this project. It was also felt that the use of etiocholanolone had an effect in modifying depression ratings.

Part B of the DRS is concerned with the physiological functioning of the patient. It was suspected during data analysis last year, and seemed even clearer this year, that the addition of this subscale score to the total DRS rating could be deceptive for this particular group of patients for whom eating and sleeping

disturbances may occur independently of mood swings. Figure 8, therefore, shows average DRS scores for the three types of radiation groups for Parts A (Attitudes and Feelings) and Part C (Observations of the Interviewer) combined. This combination of adding somewhat less depressed subjects to each type of radiation group and of omitting physiological disturbances as part of the depressive symptomatology score has resulted in much smoother curves for the accumulated data. The effect of impending death for some subjects is still apparent in the average levels on day 28. That is, the High Total Body Radiation group ranks highest on depression scores on the average, but consideration must be given to the fact that this group is composed of eight short survivors (less than 100 days postirradiation) and three long survivors; whereas the Partial Body Radiation group, which ranks lowest on day 28, is composed of five short survivors and 12 long survivors. However, in spite of these differences in survival time, there remains a very clear increase in depression for all three groups around the fourth week.

An example of clearer data is one case we have studied of an 11-year-old girl with Ewing's tumor. Her identical twin was unaffected, but was brought to the hospital to provide bone-marrow transplant and to be studied as a control. The patient received 200r total-body irradiation. Both girls were tested at weekly intervals up to 6 weeks. Figure 9 shows their respective depression ratings through day 42. It is evident that the twin who was irradiated also showed a marked increase in depression around the fourth or fifth week that was not exhibited by the healthy twin.

For the last 2 years we have modified our procedures to obtain additional psychological measures in the third and fifth weeks in addition to the fourth and sixth. We are hopeful that within another year, additional data collection will enable us to clarify this consistent finding of greater depression for all groups around the fourth week postirradiation. As the size of each of the three radiation groups is slowly enlarged, we hope to be able increasingly to separate out the effects of radiation from those of senility, the stress of hospitalization, and approaching death, on our depression rating scales, with the concomitant

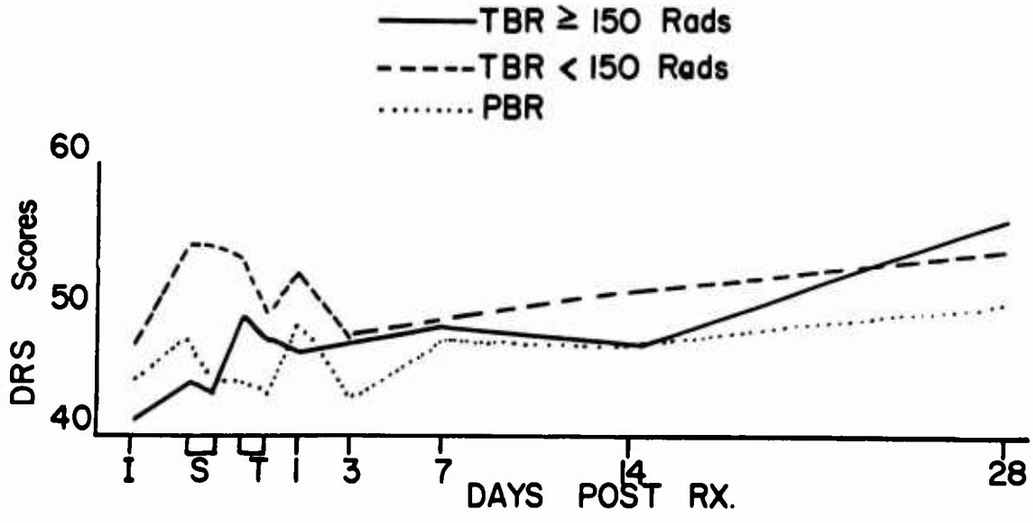


Figure 8. --Wechsler Depression Rating Scale (DRS) (Parts A and C) Mean Scores by Type of Radiation Received.

_____ 8 patients with short survival time
3 with long survival time

- - - - - - - 2 patients with short survival time
6 with long survival time

. . . . . 5 patients with short survival time
12 with long survival time

I = Initial Interview

S = Sham Radiation

T = Day of Treatment

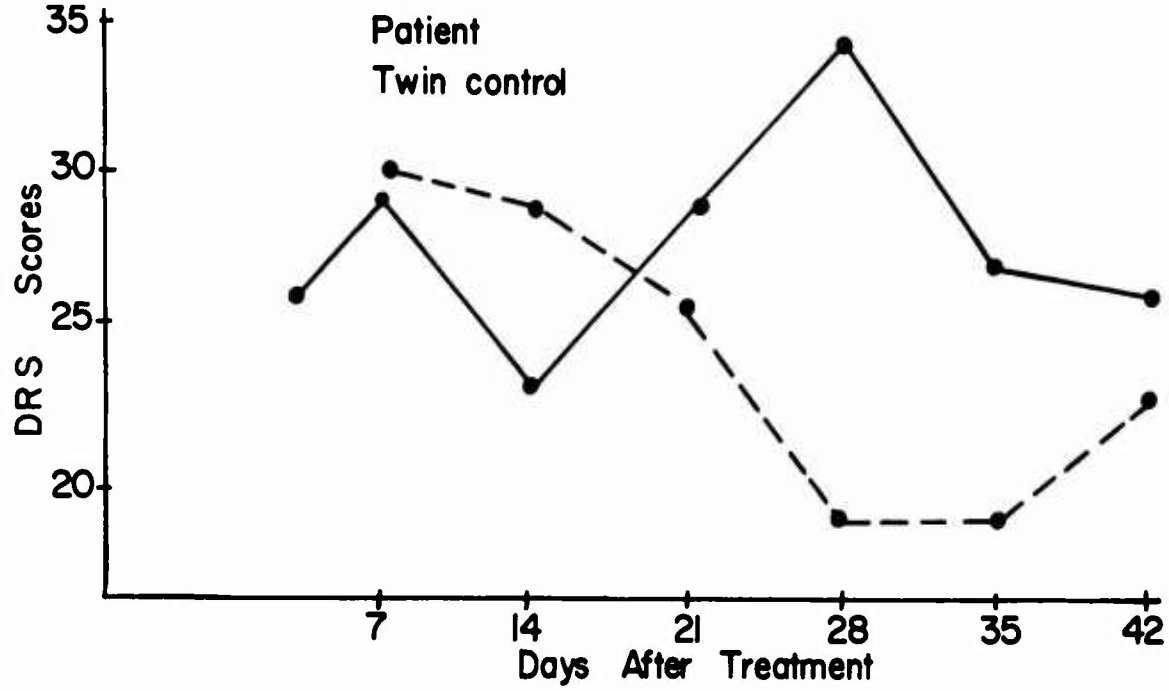


Figure 9. --Depression Rating Scale (DRS) of Young Patient and Her Twin Sister Control.

difficulties of partialing out depressive effects from the possible effects of differing doses of radiation on cognitive functioning.

Longitudinal Studies of Effects

The study of variations in levels of various effects over time for this group of terminal cancer patients has continued. In previous years, data have been presented for the early part of the study only. Table XIII and figure 10 present the data for each of the 13 measurement occasions for anxiety, hostility directed outward, hostility directed inward, and ambivalent hostility. These dimensions have all been measured by the content analysis scales designed by Gottschalk, Gleser, and Winget (76, 77).

Unlike the 16 PF anxiety scores (Factor Q_4) or Second-Order Factor 1, the construct of anxiety as measured in this content analysis system is specifically designed to tap immediate and momentary fluctuations in anxiety and fears rather than typical levels or stable personality attributes. Thus, we find that average anxiety scores as measured by verbal behavior continue to be high at the time of the initial interview and to dip both after sham radiation and after actual irradiation. The peaks at days 21 and 35 for anxiety (as well as for the three types of hostility) are based on only 11 subjects in each instance and hence must be regarded with caution until confirmed by further data.

The average scores and their fluctuations for hostility directed outward and hostility directed inward remain remarkably similar to those reported in 1969. The general trend on ambivalent hostility also resembles the levels reported in previous years. This latter scale is scored for themes about injurious, critical, or destructive thoughts and actions of others toward the self. In view of the nature of this research, it is especially reassuring to find that our subjects do not perceive the experimental situation or the personnel connected with it as in any way inimical to their best interests. This is particularly noticeable since on anxiety the patients score well above the means for normative groups; they are somewhat high on hostility directed outward and inward, but are very similar to psychiatric outpatient norms for ambivalent hostility.

TABLE XIII

AVERAGE EFFECT SCORES FOR 36 PATIENTS WITH ADVANCED METASTATIC DISEASE

			Sham		Treatment		Day							
		Initial	Pre	Post	Pre	Post	1	3	7	14	21	28	35	42
Anxiety	$\bar{X}$	1.64	1.54	1.39	1.53	1.45	1.30	1.33	1.36	1.34	1.54	1.38	1.76	1.60
	SD	.74	.91	.60	.71	.81	.67	.80	.59	.47	.45	.76	.49	.89
Hostility Out	$\bar{X}$	.92	.94	1.24	1.16	.97	1.15	1.06	1.02	.86	1.46	.91	1.23	1.09
	SD	.46	.61	.70	.77	.65	.72	.70	.55	.41	.45	.62	.55	.65
Hostility In	$\bar{X}$	.88	1.17	.96	.98	1.01	.91	.90	.97	.98	1.15	1.05	1.27	1.07
	SD	.48	.64	.60	.64	.57	.54	.46	.52	.57	.40	.67	.78	.70
Ambivalent Hostility	$\bar{X}$	.71	.75	.93	.79	.62	.78	.81	.68	.68	.81	.58	1.03	.90
	SD	.42	.49	.66	.52	.37	.59	.58	.50	.58	.48	.34	.64	.62

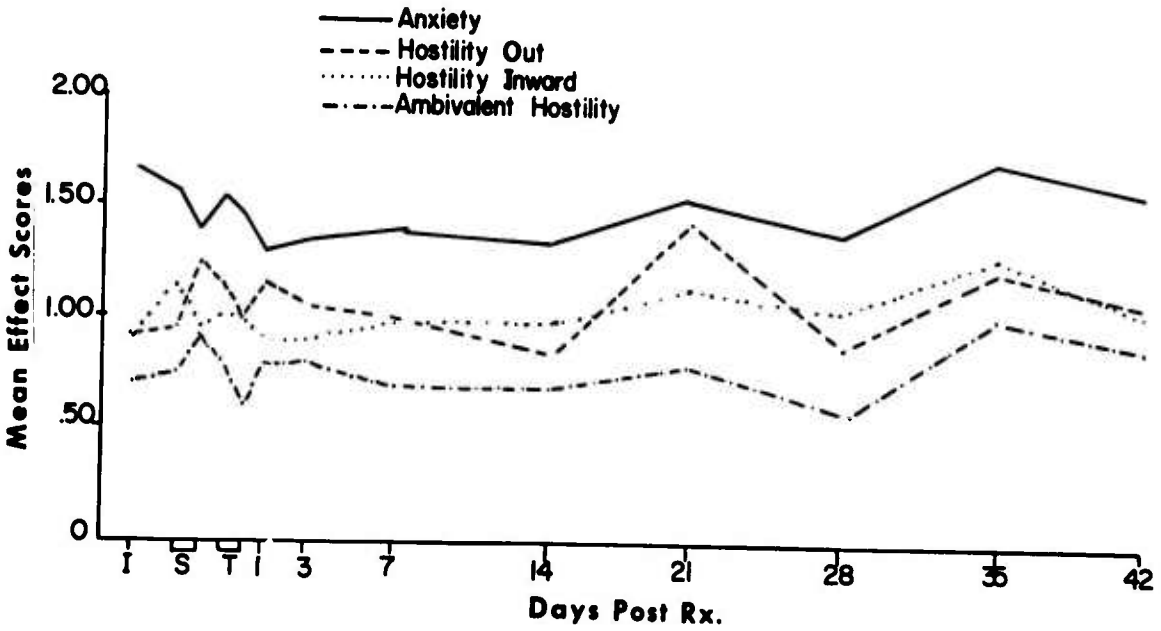


Figure 10. --Mean Effect Scores for Total Group of Patients (N = 36) for Each Testing Occasion.

I = Initial Interview

S = Sham Radiation

T = Day of Treatment

Number of Words Spoken

Table XIV and figure 11 give the accumulated data for the three radiation groups on average number of words spoken in a 5-minute time period in response to standardized instructions (77). We have hypothesized that this measure approximates an index of one's ability to carry out an assigned activity. Although the three groups start at quite different levels, with those receiving high total-body radiation (150r or more) considerably higher on the average than the other two groups, they are quite similar by day 14 and almost identical on day 28. All three groups show some decrease from preradiation to postradiation, the change being most marked for the Partial Body Irradiation group. It seems likely that the very low, initial levels and the very high 3-day levels of the Low Total-Body Radiation group are due to random sampling variation, since there is the smallest N in this group (N = 8). As reported previously, there continues to be a dip at day 28 in average number of words spoken for all three groups. It will be recalled that this is also the time period for which we report somewhat higher levels on depression.

Since the correlation between estimated IQ and word production was very high, we have also examined the average number of words spoken on each occasion for the three radiation groups differentiated by IQ. The median of 87 was used to divide the patients into high- and low-IQ groups. The verbal production data for high- and low-IQ groups for each of the three radiation dosages are given in figure 12. One can only be speculative in the interpretation of these data because of the very small N in each of the six groups. It is apparent that differences in activity as measured by verbal output are influenced by the basic intelligence of the subjects but that other variables, such as ultimate survival time, cannot be ruled out as contributing factors. It will require further data collection to untangle the intricate relationships of the effects of various doses of radiation on ability to perform this task. In this connection, table XV shows the current distribution of our sample on these two variables.

TABLE XIV

AVERAGE VERBAL OUTPUT IN FIVE MINUTES FOR EACH TESTING OCCASION BY TYPE OF RADIATION DOSE

			Sham		Treatment		Day				
		Initial	Pre	Post	Pre	Post	1	3	7	14	28
High TBR	$\bar{X}$	571	471	588	522	506	490	535	584	516	464
N = 11	SD	123	210	177	175	168	207	179	166	249	180
Low TBR	$\bar{X}$	354	428	419	452	442	464	585	526	501	572
N = 8	SD	196	204	259	231	290	221	214	242	307	287
PBR	$\bar{X}$	493	428	453	495	392	445	497	486	542	481
N = 17	AS	142	191	210	196	178	256	214	198	220	215

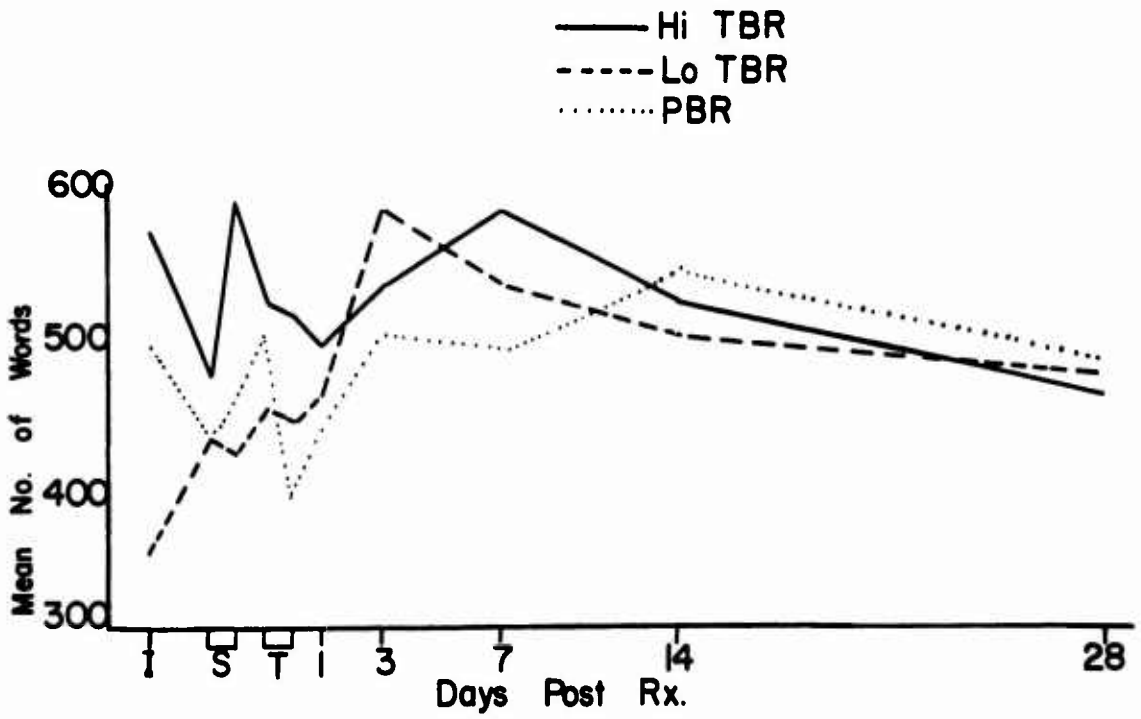


Figure 11. --Verbal Output Before and After Irradiation by Type of Radiation Received.

——— 11 patients
------- 8 patients
..... 17 patients

I = Initial Interview
S = Sham Radiation
T = Day of Treatment

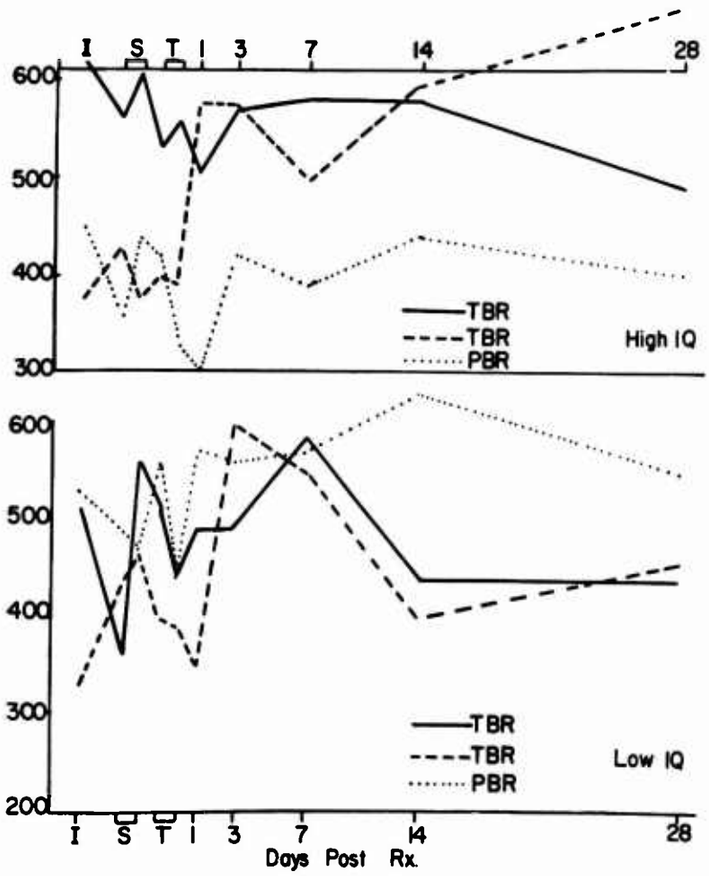


Figure 12. --Verbal Production Data for High- and Low-IQ Groups for Three Radiation Doses.

Upper Graph:
_____ 5 patients with short survival time
1 with long survival time

------- 1 patient with short survival time
3 with long survival time

..... 4 patients with short survival time
4 with long survival time

Lower Graph:
_____ 3 patients with short survival time
2 with long survival time

------- 1 patient with short survival time
3 with long survival time

..... 1 patient with short survival time
8 with long survival time

I = Initial Interview
S = Sham Radiation

TABLE XV

DISTRIBUTION OF RADIATION PATIENTS BY IQ AND SURVIVAL GROUPS

		High Survival Time	Low Survival Time
High I.Q.	High TBR	1	5
	Low TBR	3	1
	PBR	4	4
		8	10
	Total = 18		
Low I.Q.	High TBR	2	3
	Low TBR	3	1
	PBR	8	1
		13	5
	Total = 18		
	Grand Total	21	15

Hope, Health-Sickness, Human Relations

As described in earlier reports, hope, health-sickness, and human relations are all measured by the content analysis of the verbal behavior secured on each of the 13 data-collecting occasions. In general, the trends described in our 1969 report continue to hold true for the new groups of patients added this year.

As increasing data are gradually accumulated for these three variables, we hope to be able to explicate their relationship to survival time.

Cognitive Functioning

The main goal of our program of psychological evaluation has been to secure additional information regarding the effects of varying dosages of radiation on cognitive and intellectual functioning in man. A great deal of the data reported above continues to be collected and analyzed to take into account the many complex variables that may influence this multidimensional construct.

Looking at the current data first in its most general form, figure 13 indicates average cognitive impairment scores for our entire group of 36 patients for the entire study period. Days 21, 35, and 42 have been marked by an "X" to indicate that they are to be regarded as only tentative average levels since the size of the sample for these three points is only about one-third of the total group of patients. This attrition is due to death (day 42) and to the fact that two of these data collection occasions were not included on patients studied prior to 1968 (days 21 and 35).

It can be seen that for the group as a whole there is a slight rise in cognitive impairment after sham radiation with a more marked rise after actual irradiation. By day 3, the average for all subjects is at its presham and preirradiation level. There is then a slight but steady increase in intellectual dysfunction to day 21, followed by a general leveling off at averages somewhat higher than the presham and pretreatment means. From day 14 onward, however, this trend must be considered as highly speculative until more data can be accumulated.

Using seven occasions (presham, postsham, pretreatment, posttreatment, day 1, day 3, and day 7), cognitive impairment scores were ranked within the

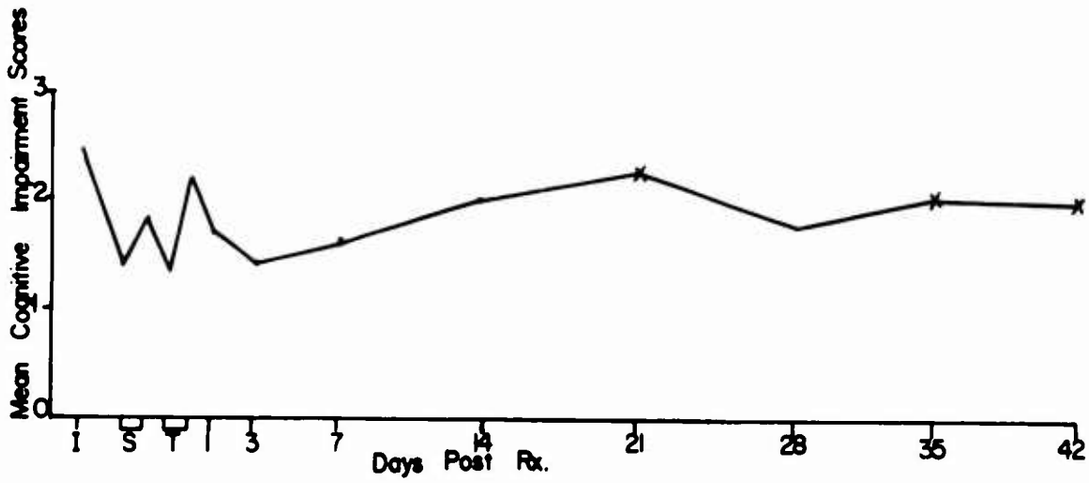


Figure 13. --Average Cognitive Impairment Scores for the Total Group of Patients (N = 36), Before and After Irradiation.

I = Initial Interview

S = Sham Radiation

T = Day of Treatment

24 patients for whom data were relatively complete. (This included three patients on whom one estimate each had been made.) These data were then submitted to the Friedman nonparametric test for matched groups. The column sum for the various radiation groups is given in table XVI. A significant difference (χ^2 = 14.47, $p < .05$, 6 d.f.) was obtained for the column sums of the ranks over all groups, pretreatment ranking lowest and post-treatment ranking highest.

Figure 14 provides the averages for cognitive impairment for the first 28 days of the study by type of radiation received. In spite of differing initial average levels, all three types of radiation groups dip to a greater or lesser degree before sham, rise slightly postsham, and are remarkably similar in showing a sharp preradiation to postradiation increase in dysfunction. All three groups tend to show a slight peak at day 14 with a downward trend on day 28. The High and Low Total-Body Radiation groups do not differ in any essential way on the average after day 7. There does seem to be a tendency for the High Total-Body Radiation group to drop from its post-treatment peak more slowly than does the Low Total-Body Radiation group. Using the same technique of rank ordering seven occasions within each of the subjects for whom data are available, we find that the preradiation to postirradiation increase was highly significant for the two Total-Body Radiation groups combined (χ^2 = 19.32, $p < .01$, 6 d.f.), but not for the Partial-Body Radiation group.

There are a number of paradoxes here. One puzzle has to do with the assumption that if cognitive impairment is affected by radiation, it should be affected more by the higher rather than by the lower doses. This we did not find to be true, and it is possible that at the doses we use we are below the threshold for picking up such differential dosage effects.

A second puzzle is finding that cognitive impairment in the Partial-Body Radiation group does not rise significantly after radiation as it does after doses of total-body radiation, but that average levels of cognitive impairment for the Partial-Body Radiation group from day 1 onward remain consistently higher than for the two Total-Body Radiation groups. Here survival time and its effect on the depression-rating scale seem pertinent as well as the average verbal output of patients which we know to be highly correlated with cognitive impairment

TABLE XVI

FRIEDMAN NONPARAMETRIC TEST FOR MATCHED GROUPS

		Sham		Treatment		Day		
		Pre	Post	Pre	Post	1	3	7
High TBR	N = 5	24	22	17	30	19	14	14
Low TBR	N = 6	14	27	24	39	20	23	21
PBR-L	N = 7	25	36	29	28	21	25	32
PBR-N/P	N = 4	13	19	7	17	19	21	16
PBR-U	N = 2	13	9	2	7	7	7	11
	Total	89	113	79	121	86	90	94

$\chi^2 = 14.47 \quad p < .05, \ 6 \text{ d.f.}$

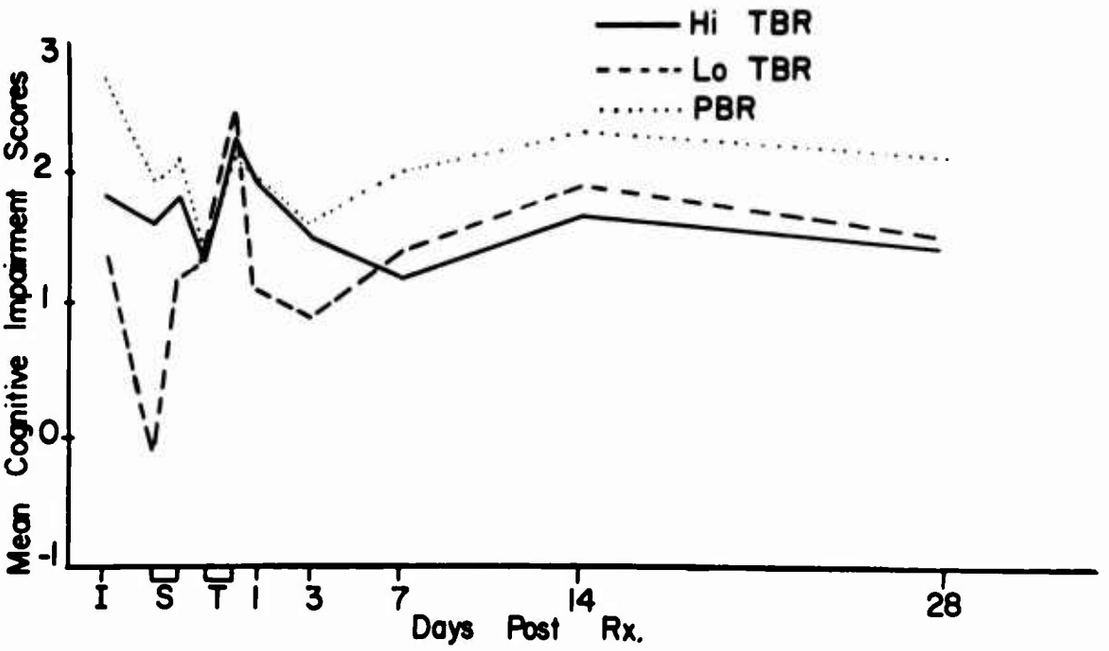


Figure 14. --Cognitive Impairment by Type of Radiation Dose.

_____	11 patients	I	= Initial Interview
-------	8 patients	S	= Sham Radiation
.....	17 patients	T	= Day of Treatment

(r = .50) and with IQ (r = .40). The Partial-Body Radiation group is composed of 12 long survival-time subjects and only five short survival-time subjects, but is fairly balanced on distribution of IQ (eight above the median and nine below) (see Table XV, p. 48). From day 3 onward, the Partial-Body Radiation groups show consistently less depression (see Figure 8) and is, in addition, lowest of the three groups on verbal output from post-treatment through day 7 (Figure 11). The high IQ Partial-Body Radiation group is far below the Total-Body Radiation group levels for average words spoken for post-treatment onward (Figure 12).

In a further attempt to elucidate these data, we have examined cognitive functioning within radiation group by high IQ and low IQ as defined earlier (i. e., above and below the median of IQ = 97). In the case of the High Total-Body Radiation group and the Partial-Body Radiation group, the data are very clear; i. e., the low IQ people manifest distinctly and consistently greater cognitive dysfunctioning than do the comparative high IQ group. For the Low Total-Body Radiation group, this relationship does not begin until after day 7. We suspect, however, that the smaller N of this group (four subjects in each IQ group) accounts for these results.

Summary

(1) There is evidence of a rise in cognitive malfunctioning immediately after radiation for all three types of radiation groups. This increase in dysfunction is especially significant for those who receive total-body radiation. This effect is transient and decreases markedly by day 3, although a slight peaking is found on day 14 postradiation.

(2) As might be expected of any measure of intellectual functioning, those with higher levels of basic intelligence respond with less dysfunction than do those with basic intellectual deficits.

(3) This finding with regard to cognitive impairment must be interpreted within the context of other variables which are specific to this particular patient group:

(a) High anxiety levels.

(b) Evidence of moderate depression throughout the period of the study.

(c) The confounding effect of impending death for some patients.

(4) New subjects added to this study in the last year were younger, less depressed, had had more years of schooling, and were better motivated than in previous years. A continuation of these improved patient characteristics should lead to more reliable and stable data and to less difficulty in separating out the effect of radiation from those of senility, the stress of hospitalization, and approaching death.

(5) Finally, it should be noted that our patients receive exceptionally thoughtful care from the research team. They freely express their emotional reactions during the 5-minute verbal samples which are part of the testing procedure. The blind coding of this verbal output by content analysis has given independent confirmation to the subjective reactions of the research team. These patients do not regard doctors, technicians, or the institution as being in any hostile, as measured by our ambivalent hostility scale. This is in contrast to other patients in the same institution who do express the feeling that the staff does not have their best interests at heart. Thus, this observation suggests the importance of extreme kindness and thoughtfulness in the care of patients receiving or exposed to radiation of any kind--neoplastic or accidental.

CASE HISTORIES

STUDY NO. 092

PATIENT: W. R.

CHART NO.: CGH No. 214-880

This patient, a 69-year-old Negro woman, was first admitted to Cincinnati General Hospital in June 1949. A left, radical mastectomy was performed which revealed adenocarcinoma of the breast with metastases to lymph nodes (SP 49-1439). She received a total tumor dose of 7,000r of 200 KV X-ray, from 17 August 1949 to 15 September 1949. In October 1949, a simple mastectomy of the right breast was performed. The pathologic examination revealed fibrocystic disease of breast (SP 49-2186). An ileotransverse colostomy was performed February 1969 and revealed metastatic carcinoma in lymph node, omentum, and ovary (SP 69-474).

She was admitted 29 June 1969, for partial-body irradiation. On 14 and 15 July 1969, she was shammed with no adverse side effects. She received 150 rads midline absorbed tissue dose (212r midline air exposure) of partial-body irradiation to the trunk on 16 July 1969. The patient tolerated the procedure well, with only mild anorexia and nausea noted. She was discharged to her home 11 August 1969, 26 days after PBR, to be followed by the Tumor Clinic.

The patient has been receiving biweekly injections of 5 FU since February 1970, with no adverse side effects. She continues to feel well, 405 days post PBR.

STUDY NO. 093

PATIENT: T. M.

CHART NO.: CRC No. 194-572

This patient, a 9-year-old white boy, was admitted to Reed Memorial Hospital, Richmond, Indiana, on 7 April 1969. Three weeks prior to admission, his mother noted a marble-sized nodule on his left scapula. A diagnosis of Ewing's tumor was made. He received 6,000r to the left scapula from 10 April 1969 to 22 May 1969.

On 11 September 1969, the patient was admitted to Children's Hospital, Cincinnati, Ohio, for total-body radiation. He was given sham irradiation on 16 September 1969, with no adverse side effects.

He was treated on 17 September 1969, with 150 rads midline absorbed tissue dose (208r midline air exposure) of total-body irradiation. One hour after therapy, emesis began. The vomiting lasted for 6 hours and then ceased. Spontaneous epistaxis occurred 21 days post TBR. Platelets had dropped to 39,000. Twelve units of platelets in two infusions of six each were required to control epistaxis. On 13 October 1969, 26 days post TBR, he experienced chills and fever; and his WBC dropped to a low of 200/mm.^{3} On antibiotic therapy, his temperature returned to normal; and he felt entirely well. His temperature rose again 37 days post TBR, and he again responded to antibiotic therapy.

The patient was discharged to his home 14 November 1969, 58 days post TBR. On day of discharge, his hemogram was a follows: Hct. 35%, platelets 350,000, and WBC 2,500/mm.^{3}

He continues to do well 198 days post TBR.

STUDY NO. 094

PATIENT: M. J.

CHART NO.: CGH No. 292-8-33

This 67-year-old Negro woman was first admitted to Cincinnati General Hospital on 21 May 1969 with a 6-month history of soft masses over both supraclavicular areas and intermittent "aching pain." She was known to have diabetes mellitus and degenerative osteoarthritis.

On 25 June 1969, an exploratory thoracotomy revealed an inoperable papillary adenocarcinoma of the lungs (SP 69-1963). She received a total tumor dose of 4,000r, Cobalt-60, completed on 20 August 1969.

The patient was readmitted on 21 October 1969 and given sham irradiation. She received 150 rads midline absorbed tissue dose (237r midline air exposure) of partial-body radiation, from base of neck to pubis, on the next day. She had no adverse side effects and was discharged to her home 2 days post PBR radiation to be followed in the Tumor Clinic.

She continues to do well 307 days post partial-body radiation.

STUDY NO. 095

PATIENT: A. C.

CHART NO.: CGH No. 128-870

This patient, a 58-year-old Negro woman, was admitted 25 October 1967 with a history of rectal bleeding for 2 to 3 months. A low anterior resection and cecostomy on 2 November 1967 revealed adenocarcinoma of the sigmoid colon with metastases to lymph nodes (SP 67-3689).

On 3 November 1969, the patient was admitted for marrow transplant and total-body radiation. She had sham irradiation on 3 and 4 November 1969. The next day approximately 500 cc. of bone marrow were aspirated with ease from the posterior and anterior iliac crests and sternum. The patient received 200 rads midline absorbed tissue dose (295r midline air exposure) of total-body radiation. She experienced moderate nausea and vomiting for approximately an hour. After irradiation, the bone marrow, containing 3.07×10^9 cells of 97 percent viability, was infused. On 14 November 1969, she was discharged to her home to be followed by the Tumor Clinic and was reported to be feeling well 176 days later.

STUDY NO. 096

PATIENT: A. S.

CHART NO.: CGH No. 503-2-83

This 43-year-old Negro man was readmitted to Cincinnati General Hospital on 1 December 1969 for total-body irradiation. He had had a cecostomy for relief of acute intestinal obstruction on 17 June 1969. On 11 July 1969, a left colectomy, ureteral implantation, and partial hepatic lobectomy were done. The pathologic examination revealed adenocarcinoma of the colon with metastases to the mesentery and liver (SP 69-2136).

The patient was given sham radiation on 1 December 1969. The next day he received 100 rads midline absorbed tissue dose (172r midline air exposure) of total-body irradiation. He tolerated the procedure well.

The patient was discharged to his home on 3 December 1969, to be followed in the Surgical Clinic. He continues to do well 267 days post total-body irradiation.

STUDY NO. 097

PATIENT: E. C.

CHART NO.: CGH No. 354-9-60

The patient, a 67-year-old Negro man, received 300 rads midline absorbed tissue dose (471r midline air exposure) of partial-body radiation to the upper body on 7 November 1968 for metastatic lung carcinoma (Pancoast's tumor) (SP 68-1243).

He was readmitted on 15 December 1969 because of continued pain in his right arm. He received sham radiation 15 December 1969. On 16 December 1969, the patient was given 100 rads midline absorbed tissue dose (148r midline air exposure) of total-body radiation. He experienced anorexia for the following 15 hours. There were no other adverse side effects.

The patient was discharged to his home on 17 December 1969, one day post-radiation, to be followed by the Tumor Clinic.

On 13 June 1970, the patient reentered Cincinnati General Hospital due to continued severe right-arm pain. An unsuccessful percutaneous chordotomy was performed 16 July 1970. Because of his inability to care for himself, he was transferred to a nursing home on 7 August 1970, where he died 5 days later, 229 days post TBR.

STUDY NO. 098

PATIENT: R. S.

CHART NO.: CGH No. 374-083

This patient, a 45-year-old Negro woman, was admitted 6 November 1968, with a chief complaint of anorexia and right lower quadrant pain of approximately 5 months' duration. A barium enema done on 8 November 1968, revealed probable carcinoma of the proximal ascending colon. A right hemi-colectomy with ileotransverse colostomy was performed on 15 November 1968, and revealed adenocarcinoma of the cecum with serosal extension and metastases to five lymph nodes (SP 68-3597).

She was admitted to Cincinnati General Hospital on 26 January 1970, for total-body irradiation and marrow transplant. She also received sham irradiation on this date. On 27 January 1970, 500 cc. of bone marrow were aspirated with ease from the posterior and anterior iliac crests and from the sternum. Following the aspiration, the patient received 200 rads midline absorbed tissue dose (324r midline air exposure) of total-body irradiation. She experienced three episodes of vomiting after treatment. The same afternoon, the bone marrow containing 7.42×10^9 cells and 98 percent viability was infused. On 30 January 1970, the patient was discharged to her home, to be followed in the Tumor Clinic. The patient continues to do well 119 days post TBR.

STUDY NO. 099

PATIENT: P. D.

CHART NO.: CGH No. 106-720

This patient, a 47-year-old Negro man, was admitted to Cincinnati General Hospital 23 August 1969 with abdominal pain, anorexia, and a 10-pound weight loss in 3 weeks. Exploratory laparotomy was performed on 18 September 1969, with a diagnosis of metastatic pancreatic adenocarcinoma involving lymph nodes (SP 69-2907).

On 2 March 1970, this patient was readmitted for whole-body radiation and marrow transplant due to increasing epigastric and back pain. He had sham radiation the next day. On 3 March 1970, 500 cc. of bone marrow were easily aspirated from the posterior and anterior iliac crests and the sternum. After the aspiration, the patient received 230 rads midline absorbed tissue dose (332r midline air exposure) of total-body radiation. He experienced only slight nausea for about an hour. Bone marrow containing 5.32×10^9 cells and 95 percent viability was infused. He tolerated the procedure well.

This patient was again admitted on 27 March 1970 due to generalized weakness and increasing pain. He continued to deteriorate rapidly and died on 3 April 1970, 31 days post TBR.

STUDY NO. 100

PATIENT: J. D.

CHART NO.: CGH No. 49688

This patient, a 76-year-old Negro man, was admitted 21 March 1969 with a chief complaint of diarrhea for 2 months. Sigmoidoscopy and biopsy on 24 March 1969 revealed adenocarcinoma of the large intestine (SP 69-900). An abdominal-perineal resection was performed on 2 April 1969 and revealed adenocarcinoma of the rectum, metastiatic to lymph nodes (SP 69-1021).

On 11 March 1970, he was admitted to Cincinnati General Hospital for partial-body radiation. He received sham radiation on 16 March 1970 with no adverse side effects. On 17 March 1970, the patient received 300 rads midline absorbed tissue dose (479r midline air exposure) of partial-body radiation to the lower body. He experienced one episode of vomiting approximately 30 minutes following treatment. He was discharged to his home 13* March 1970, to be followed by the Tumor Clinic.

He continues to do well 169 days post PBR.

*Editor questions date.

STUDY NO. 101

PATIENT: M. H.

CHART NO.: CGH No. 167-1-51

This 76-year-old Negro man was admitted to Cincinnati General Hospital on 19 December 1969 with a 2- to 3-year history of intermittent rectal bleeding and continuous rectal bleeding for the last 3 weeks. A sigmoidoscopy was performed on 22 December 1969 and revealed adenocarcinoma of the large intestine (SP 69-3976). On 5 January 1970, an abdominoperineal resection was performed. The biopsy showed colloid adenocarcinoma of the rectum extending into the anus and pericolic fat tissue with metastasis to five out of nine lymph nodes (SP 70-35).

The patient was readmitted on 17 April 1970 for partial-body irradiation. He was given sham irradiation on 20 April 1970 with no adverse side effects. The next day he received 257 rads midline absorbed tissue dose (559r midline air exposure) of partial-body irradiation to the lower body. He experienced nausea and vomiting near the end of the treatment and became nauseated again the following morning.

The patient was discharged 22 April 1970 to his home to be followed by the Tumor Clinic. He continues to do well 124 days PBR.

STUDY NO. 102

PATIENT: W. W.

CHART NO.: CGH No. 362-7-77

This patient, a 49-year-old Negro man, was admitted to Cincinnati General Hospital on 26 August 1969, because of shortness of breath and lower left, lateral chest pain. Thoracentesis was performed 27 August 1969, and adenocarcinoma (SP 69-2661) was found in the cells of the pleural effusion.

The patient was readmitted 16 October 1969 for thoracentesis and additional workup. Nitrogen mustard was instilled into the left hemithorax on 31 October 1969. The patient was given sham radiation on 27 April 1970 with no adverse side effects.

He was treated 28 April 1970, with 200 rads midline absorbed tissue dose (307r midline air exposure) of partial-body radiation to the trunk. Immediately following therapy, he became nauseated and vomited once. The patient was discharged on 30 April 1970.

Due to increasing weakness and a hematocrit of 20 percent, he was admitted to Cincinnati General Hospital on 5 May 1970. The patient's condition continued a downhill course, and he died on 20 May 1970, 22 days post PBR.

STUDY NO. 103

PATIENT: R. S.

CHART NO.: CGH No. 374-083

This 45-year-old Negro woman, with known metastatic adenocarcinoma of the cecum (SP 68-3597), was admitted to Cincinnati General Hospital 21 May 1970, for partial-body radiation. In January 1970, she received 200 rads of whole-body radiation with an autologous bone-marrow transplant. Her abdominal discomfort was briefly relieved, but has returned. The patient was shammed 25 May 1970 and treated on 26 May 1970 with 300 rads midline absorbed tissue dose (479r midline air exposure) of partial-body irradiation to the lower body. She vomited once following treatment, but otherwise tolerated it well and was discharged 27 May 1970, to be followed in the Tumor Clinic.

On 21 July 1970, 56 days post PBR, because of increased right lower quadrant pain, weekly injections of 5 FU were begun. She received a total of eight injections. She continues to do well, 163 days post PBR.

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APPENDIX A

PROTOCOL FOR CHROMOSOME CULTURE

1. A 10 ml. syringe is moistened with 0.1 ml. heparin (1 ml. = 5,000 U.S.P. units containing 1% benzyl alcohol) and 10 ml. venous blood are aspirated under sterile conditions.

2. Blood is then transferred to a sterile screwcap tube. It is mixed gently, and the red cells are allowed to sediment while under refrigeration for 1 hour.

3. 0.5 to 1.0 ml. leukocyte rich plasma is added to four sterile, disposable flasks containing 4 to 5 ml. of the following media: 80% Minimum Essential Media, * 15% Fetal Bovine Serum, 2.4% phytohemagglutinin, 1.2% l-glutamine, and 1% penicillin and streptomycin.

4. The culture is incubated at 37° C. for 46 to 50 hours at ambient pO_2. No CO_2 is added to the system.

5. Then, 0.1 ml. of 0.0004% colchicine in Hank's** balanced salt solution is added to each culture which is returned to the incubator for 1 to 2 hours.

6. The flasks are agitated, and the contents emptied into a serologic tube which is centrifuged for 2 minutes in an Adams Sero-Fuge.

7. The supernatant is aspirated and discarded. The cells are washed with 37° C. 0.7% sodium citrate and placed in a 37° C. water bath for 4 to 7 minutes, then centrifuged as in step 6.

8. The supernatant is then aspirated and discarded. Without disturbing the cell button, one adds 1 to 2 ml. Carnoy's fixative (3 parts Methanol to 1 part Glacial Acetic Acid) and allows the button to stand 30 minutes.

9. The cells are resuspended and centrifuged as before.

10. Steps 8 and 9 may be repeated as needed, usually twice.

11. Sufficient Carnoy's fixative is added to obtain an opalescent appearance, about 0.5 ml.

*Gibco, Grand Island Biological Co., Grand Island, New York.
**Difco Pharmaceuticals, Detroit, Michigan.

12. Slides are prepared by dropping 3 to 5 drops of cell suspension on clean slides which have been wet in cold distilled water, igniting them momentarily in an alcohol burner.

13. They are stained with 1:10 Giemsa stain for 14 minutes.

14. The slides are then rinsed with acetone twice, acetone: xylol (1:1) once and then placed in 100% xylol until all are ready to mount.

15. The slides are mounted by adding 1 drop*** Permount and a coverslip.

***Fisher Scientific, Fairlawn, New Jersey.

APPENDIX B

DOSIMETRY:

1. Total-Body Radiation, Cobalt-60.

The radiation is delivered by a Cobalt-60 Teletherapy Unit under the following exposure conditions:

The radiation beam is directed horizontally at a wall 338 cm. away with the patient midline at 282 cm. from the source. The beam area for the 50-percent isodose curve at the patient midline distance is a square approximately 72 cm. by 72 cm. (Figure 15). The patient is placed in a sitting position with legs raised and head tilted slightly forward. Tne irradiation is given by delivering half of the specified exposure laterally through one side of the patient. The patient is then turned, and the other half exposure delivered laterally through the other side.

The variation of air exposure with distance from the source was determined with a Victoreen 25r chamber. The results indicated no departure from the inverse square-law relationship for distances used in the study. Therefore, no correction was required for a possible dose contribution to the patient due to backscatter from the wall.

Preliminary measurements were made in a masonite phantom using dosimeters placed on lateral surfaces and at the midline of the head, trunk, and knee portions of the phantom. If the midline doses to the trunk, head, and knees are compared, the maximum variation in these doses is about 16 percent.

The exposure to the patient was determined as follows. The percentage depth dose at different depths for a 400 cm.^{2} field area and a source-skin distance of 80 cm. is given by H. E. Johns, "The Physics of Radiology," Charles C. Thomas, Springfield, Illinois. The depth dose at the greater source-skin distances used for the patients was found by multiplying the depth doses at 80 cm. by the "F" factor postulated by Mayneord and Lamerton (Brit. J. Radiol. 14:255, 1941).

$$F = \frac{(D_d)_{f_2}}{(D_d)_{f_1}} = \left[\frac{f_2}{f_1} \times \frac{f_1 + d}{f_2 + d} \right]^2$$

Where: f_1 and f_2 are source-skin distances.

d is the depth.

By using the corrected depth dose at the patient midline (one-half lateral dimension of the trunk) and a conversion factor of 0.97 rads per roentgen for Cobalt gamma radiation, the surface dose and midline air exposure required to give a desired midline absorbed dose in rads were calculated.

A direct comparison of the calculated and measured (phantom) doses was made for one patient who had the same lateral trunk dimensions as the phantom. The relative depth dose for each lateral exposure to this patient is given in figure 16. The doses indicated by crosses are measurements made in the phantom and compare quite well with the calculated doses. The combined dose of the two radiation fields is also given in this figure and shows a good homogeneous dose distribution through this patient. The maximum variation in lateral dose distribution was $\pm$ 13 percent for one patient having a lateral trunk dimension of 36 cm.

2. Partial-Body Radiation.

In the individuals receiving partial-body radiation, the teletherapy collimator is used to restrict the beam. The isodose curves for this latter case is shown in figure 17. The relative dose for upper body radiation is shown in the figure. These phantom measurements were determined with thermoluminescent dosimeters. For partial-body radiation, the xiphoid was used as the boundary. This technique is similar to that described by Hanse, Michaelson, and Howland (The Biological Effects of Upper Body X-irradiation of Beagles, UR 580, University of Rochester Atomic Energy Project, 1960).

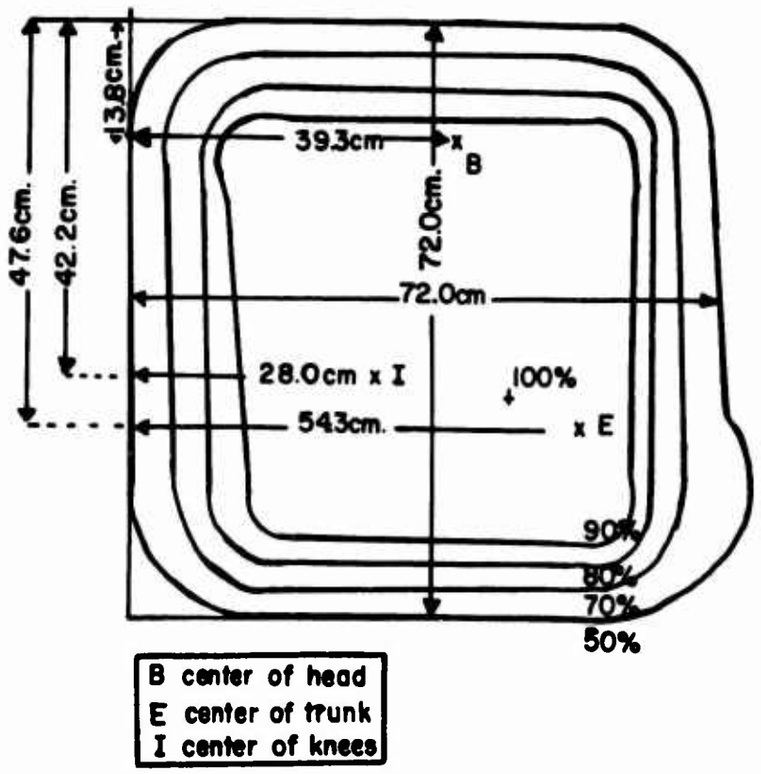

Figure 15. --Isodose Curves for Radiation Technique Employed With Patient Midline at 282 cm. From Source.

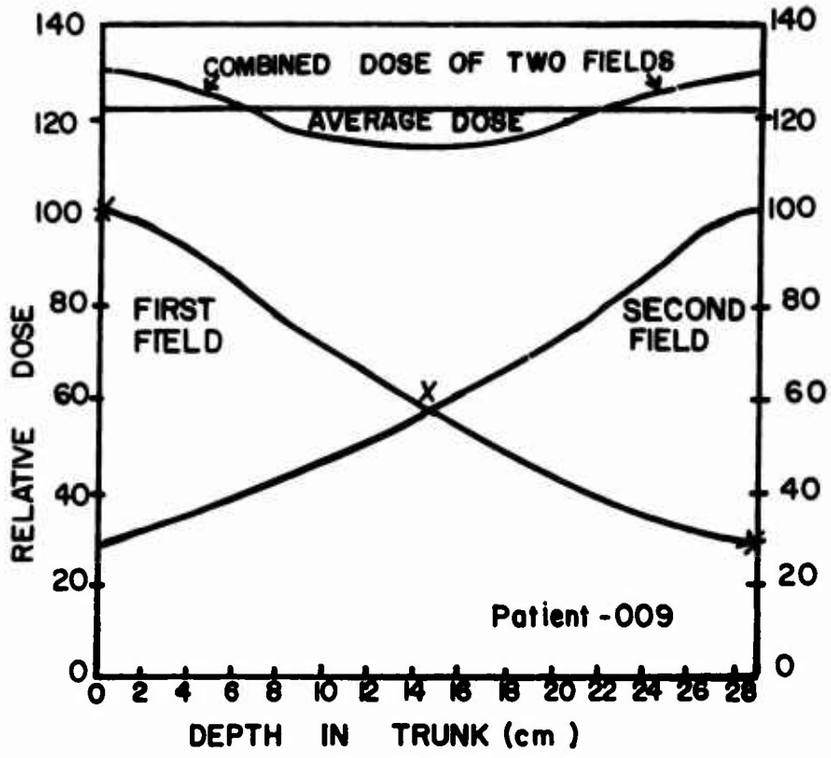

Figure 16. --Relative Depth Dose for Each Lateral Radiation Exposure.

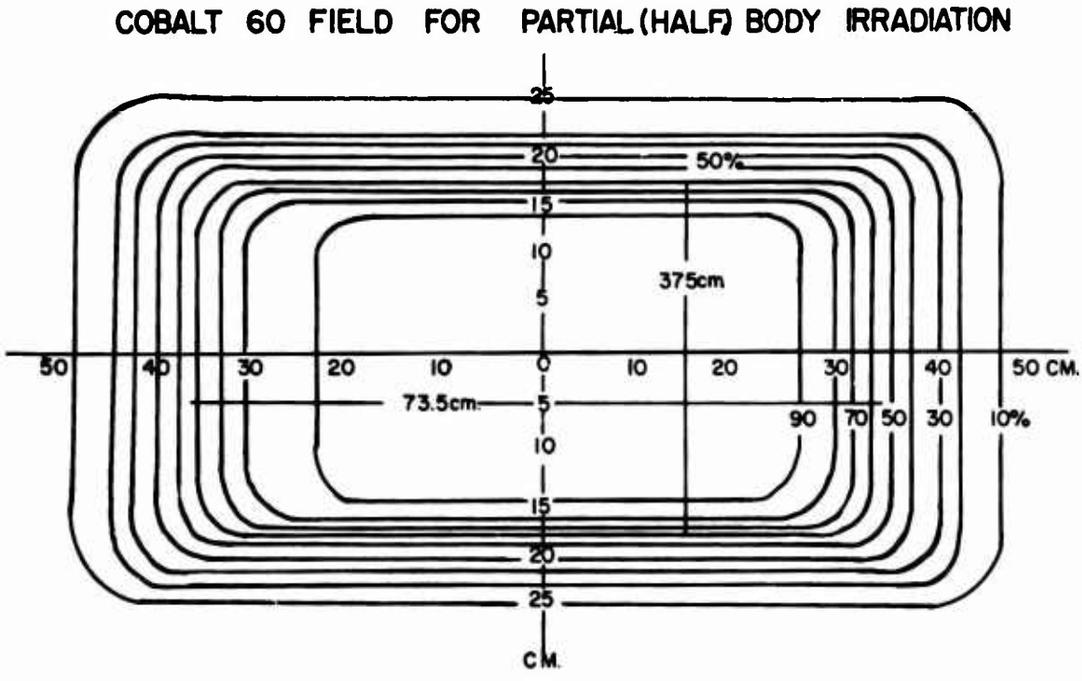

Figure 17. --Cobalt-60 Field for Partial(Half)-Body Irradiation.

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